Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/US05/005193

International filing date: 18 February 2005 (18.02.2005)

Document type: Certified copy of priority document

Document details: Country/Office: US
Number: 60/548,886
Filing date: 02 March 2004 (02.03.2004)

Date of receipt at the International Bureau: 18 April 2005 (18.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse

130366

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

April 01, 2005

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE.

APPLICATION NUMBER: ***60/548,886***
FILING DATE: ***March 02, 2004***
RELATED PCT APPLICATION NUMBER: ***PCT/US05/05193***

Certified by

Jon W. Dudas

Under Secretary of Commerce
for Intellectual Property
and Director of the United States
Patent and Trademark Office

PTO/SB/16 (05-03)
Approved for use through 4/30/2003. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

Express Mail Label No.

INVENTOR(S)		
Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Yardena	Samuels	Baltimore, Maryland
Victor	Velculescu	Dayton, Maryland

☒ *Additional inventors are being named on the 1 separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Mutations of the PIK3CA Gene in Human Cancers

CORRESPONDENCE ADDRESS

Direct all correspondence to:

☒ Customer Number 22907 → *Place Customer Number Bar Code Label here*

OR *Type Customer Number here*

☐ Firm or Individual Name					
Address					
Address					
City		State		ZIP	
Country		Telephone		Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☒ Specification *Number of Pages* 36 ☐ CD(s), Number

☒ Drawing(s) *Number of Sheets* 3 ☒ Other (specify) Paper Sequence Listing

☒ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☒ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

FILING FEE AMOUNT ($)

☒ The Director is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 19-0733 — 80

☐ Payment by credit card. Form PTO-2038 is attached.

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.

☒ Yes, the name of the U.S. Government agency and the Government contract number are: NIH-CA43460; NIH-CA62924.

Respectfully submitted,

SIGNATURE

TYPED or PRINTED NAME Sarah A. Kagan

TELEPHONE 202.824.3161

Date 3/2/04

REGISTRATION NO. *(if appropriate)* 32,141

Docket Number: 001107.00428

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

PROVISIONAL APPLICATION COVER SHEET

Additional Page

PTO/SB/16 (05-03)
Approved for use through 4/30/2003. OMB 0651-0032
Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Docket Number	001107.00428

INVENTOR(S)/APPLICANT(S)

Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
Kenneth W.	Kinzler	Bel Air, Maryland
Bert	Vogelstein	Baltimore, Maryland

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

MUTATIONS OF THE PIK3CA GENE IN HUMAN CANCERS

[01] This application was made using funds provided by the United States government under grant nos. NIH-CA 62924 and NIH-CA 43460. The United States government therefore retains certain rights in the invention.

FIELD OF THE INVENTION

[02] The invention relates to the fields of diagnostic tests and therapeutic methods for cancer.

BACKGROUND OF THE INVENTION

[03] PI3Ks are lipid kinases that function as signal transducers downstream of cell surface receptors and mediate pathways important for cell growth, proliferation, adhesion, survival and motility (*1, 2*). Although increased PI3K activity has been observed in many colorectal and other tumors (*3, 4*), no intragenic mutations of PI3K have been identified.

[04] Members of the PIK3 pathway have been previously reported to be altered in cancers, for example, the PTEN tumor suppressor gene (*15, 16*), whose function is to reverse the phosphorylation mediated by PI3Ks (*17, 18*). Reduplication or amplification of the chromosomal regions containing PIK3CA and AKT2 has been reported in some human cancers (*2, 19, 20*), but the genes that are the targets of such large-scale genetic events have not been and cannot easily be defined.

BRIEF SUMMARY OF THE INVENTION

[05] In a first embodiment a method is provided for assessing cancer in a human tissue suspected of being cancerous of a patient. A non-synonymous,

intragenic mutation in a PIK3CA coding sequence is detected in a body sample of a human suspected of having a cancer. The human is identified as likely to have a cancer if a non-synonymous, intragenic mutation in PIK3CA coding sequence is determined in the body sample.

[06] In a second embodiment of the invention a method is provided for inhibiting progression of a tumor in a human. An antisense oligonucleotide or antisense construct is administered to a tumor. The antisense oligonucleotide or RNA transcribed from the antisense construct is complementary to mRNA transcribed from PIK3CA. The amount of p110α protein expressed by the tumor is thereby reduced.

[07] Another embodiment of the invention provides a method of inhibiting progression of a tumor in a human. siRNA comprising 19 to 21 bp duplexes of a human PIK3CA mRNA with 2 nt 3' overhangs are administered to the human. One strand of the duplex comprises a contiguous sequence selected from mRNA transcribed from PIK3CA (SEQ ID NO: 2). The amount of p110α protein expressed by the tumor is thereby reduced.

[08] According to another aspect of the invention a method is provided for inhibiting progression of a tumor. A molecule comprising an antibody binding region is administered to a tumor. The antibody binding region specifically binds to PIK3CA (SEQ ID NO: 3).

[09] Another embodiment of the invention provides a method of identifying candidate chemotherapeutic agents. A wild-type or activated mutant p110α (SEQ ID NO: 3) is contacted with a test compound. p110α activity is then measured. A test compound is identified as a candidate chemotherapeutic agent if it inhibits p110α activity.

[10] Still another embodiment of the invention is a method for delivering an appropriate chemotherapeutic drug to a patient in need thereof. A non-synonymous, intragenic mutation in a PIK3CA coding sequence (SEQ ID NO:

1) is determined in a test tissue of a patient. A p110α inhibitor is administered to the patient.

[11] An additional aspect of the invention provides a set of one or more primers for amplifying and/or sequencing PIK3CA. The primers are selected from the group consisting of forward primers, reverse primers and sequencing primers. The forward primers are selected from the group consisting of: SEQ ID NO: 6 to 158; the reverse primers are selected from the group consisting of: SEQ ID NO: 159 to 310; and the sequencing primers are selected from the group consisting of: SEQ ID NO: 311 to 461.

BRIEF DESCRIPTION OF THE DRAWINGS

[12] Fig. 1. Detection of mutations in of PIK3CA. Representative examples of mutations in exons 9 and 20. In each case, the top sequence chromatogram was obtained from normal tissue and the three lower sequence chromatograms from the indicated tumors. Arrows indicate the location of missense mutations. The nucleotide and amino acid alterations are indicated above the arrow.

[13] Fig. 2. Distribution of mutations in PIK3CA. Arrows indicate the location of missense mutations, and boxes represent functional domains (p85BD, p85 binding domain; RBD, Ras binding domain; C2 domain; Helical domain; Kinase domain). The percentage of mutations detected within each region in cancers is indicated below.

[14] Figs. 3A-3C. Increased lipid kinase activity of mutant p110α. NIH3T3 cells were transfected with empty vector or with vector constructs containing either wild-type p110α or mutant p110α (H1047R) as indicated above the lanes. Immunoprecipitations were performed either with control IgG or anti-p85 polyclonal antibodies. (Fig. 3A) Half of the immunoprecipitates were subjected to a PI3-kinase assay using phosphatidylinositol as a substrate. "PI3P" indicates the position of PI-3-phosphate determined with standard phosphatidyl markers and "Ori" indicates the origin. (Fig. 3B) The other half

of the immunoprecipitates was analyzed by western blotting with anti-p110α antibody. (Fig. 3C) Cell lysates from transfected cells contained similar amounts of total protein as determined by western blotting using an anti-α-tubulin antibody. Identical results to those shown in this figure were observed in three independent transfection experiments.

DETAILED DESCRIPTION OF THE INVENTION

[15] The clustering of mutations within PIK3CA make it an excellent marker for early detection or for following disease progression. Testing focused in the clustered regions will yield most of the mutant alleles.

[16] The human PIK3CA coding sequence is reported in the literature and is shown in SEQ ID NO: 1. This is the sequence of one particular individual in the population of humans. Humans vary from one to another in their gene sequences. These variations are very minimal, sometimes occurring at a frequency of about 1 to 10 nucleotides per gene. Different forms of any particular gene exist within the human population. These different forms are called allelic variants. Allelic variants often do not change the amino acid sequence of the encoded protein; such variants are termed synonymous. Even if they do change the encoded amino acid (non-synonymous), the function of the protein is not typically affected. Such changes are evolutionarily or functionally neutral. When human PIK3CA is referred to in the present application all allelic variants are intended to be encompassed by the term. The sequence of SEQ ID NO: 1 is provided merely as a representative example of a wild-type human sequence. The invention is not limited to this single allelic form of PIK3CA. For purposes of determining a mutation, PIK3CA sequences determined in a test sample can be compared to a sequence determined in a different tissue of the human. A difference in the sequence in the two tissues indicates a somatic mutation. Alternatively, the sequence determined in a PIK3CA gene in a test sample can be compared to the sequence of SEQ ID NO: 1. A difference between the test sample

sequence and SEQ ID NO: 1 can be identified as a mutation. Tissues suspected of being cancerous can be tested, as can body samples that may be expected to contain sloughed-off cells from tumors or cells of cancers. Suitable body samples for testing include blood, serum, plasma, sputum, urine, stool, nipple aspirate, saliva, and cerebrospinal fluid.

[17] Mutations in PIK3CA cluster in exons 9 (SEQ ID NO: 4) and 20 (SEQ ID NO: 5). Other mutations occur, but these two exons appear to be the hotspots for mutations. Many mutations occur in PIK3CA's helical domain (nt 1567-2124 of SEQ ID NO: 2) and in its kinase domain (nt 2095-3096 of SEQ ID NO: 2). Fewer occur in PIK3CA's P85BD domain (nt 103-335 of SEQ ID NO: 2). Mutations have been found in exons 1, 2, 4, 5, 7, 9, 13, 18, and 20. Any combination of these exons can be tested, optionally in conjunction with testing other exons. Testing for mutations can be done along the whole coding sequence or can be focused in the areas where mutations have been found to cluster. Particular hotspots of mutations occur at nucleotide positions 1624, 1633, 1636, and 3140 of PIK3CA coding sequence.

[18] PIK3CA mutations have been found in a variety of different types of tumors. Thus any of a variety of tumors can be tested for PIK3CA mutations. These tissues include, without limitation: colorectal tissue, brain tissue, gastric tissue, breast tissue, and lung tissue.

[19] Any type of intragenic mutation can be detected. These include substitution mutations, deletion mutations, and insertion mutations. The size of the mutations is likely to be small, on the order of from 1 to 3 nucleotides. Mutations which can be detected include, but are not limited to G1624A, G1633A, C1636A, A3140G, G113A, T1258C, G3129T, C3139T, and G2702T. Any combination of these mutations can be tested.

[20] The mutations that are found in PIK3CA appear to be activating mutations. Thus therapeutic regimens involving inhibition of p110α activity or expression can be used to inhibit progression of a tumor in a human.

Inhibitory molecules which can be used include antisense oligonucleotides or antisense constructs, a molecule comprising an antibody binding region, and siRNA molecules. Molecules comprising an antibody binding region can be full antibodies, single chain variable regions, antibody fragments, antibody conjugates, etc. The antibody binding regions may but need not bind to epitopes contained within the kinase domain (nt 2095-3096 of SEQ ID NO: 2) of PIK3CA, the helical domain (nt 1567-2124 of SEQ ID NO: 2) of PIK3CA, or the P85BD domain (nt 103-335 of SEQ ID NO: 2) of PIK3CA.

[21] Antisense constructs, antisense oligonucleotides, RNA interference constructs or siRNA duplex RNA molecules can be used to interfere with expression of PIK3CA. Typically at least 15, 17, 19, or 21 nucleotides of the complement of PIK3CA mRNA sequence are sufficient for an antisense molecule. Typically at least 19, 21, 22, or 23 nucleotides of PIK3CA are sufficient for an RNA interference molecule. Preferably an RNA interference molecule will have a 2 nucleotide 3' overhang. If the RNA interference molecule is expressed in a cell from a construct, for example from a hairpin molecule or from an inverted repeat of the desired PIK3CA sequence, then the endogenous cellular machinery will create the overhangs. siRNA molecules can be prepared by chemical synthesis, in vitro transcription, or digestion of long dsRNA by Rnase III or Dicer. These can be introduced into cells by transfection, electroporation, or other methods known in the art. See Hannon, GJ, 2002, RNA Interference, *Nature* 418: 244-251; Bernstein E et al., 2002, The rest is silence. *RNA 7:* 1509-1521; Hutvagner G et al., RNAi: Nature abhors a double-strand. *Curr. Opin. Genetics & Development 12:* 225-232; Brummelkamp, 2002, A system for stable expression of short interfering RNAs in mammalian cells. *Science 296:* 550-553; Lee NS, Dohjima T, Bauer G, Li H, Li M-J, Ehsani A, Salvaterra P, and Rossi J. (2002). Expression of small interfering RNAs targeted against HIV-1 rev transcripts in human cells. *Nature Biotechnol.* **20**:500-505; Miyagishi M, and Taira K. (2002). U6-promoter-driven siRNAs with four uridine 3' overhangs efficiently suppress

targeted gene expression in mammalian cells. *Nature Biotechnol.* **20**:497-500; Paddison PJ, Caudy AA, Bernstein E, Hannon GJ, and Conklin DS. (2002). Short hairpin RNAs (shRNAs) induce sequence-specific silencing in mammalian cells. *Genes & Dev.* **16**:948-958; Paul CP, Good PD, Winer I, and Engelke DR. (2002). Effective expression of small interfering RNA in human cells. *Nature Biotechnol.* **20**:505-508; Sui G, Soohoo C, Affar E-B, Gay F, Shi Y, Forrester WC, and Shi Y. (2002). A DNA vector-based RNAi technology to suppress gene expression in mammalian cells. *Proc. Natl. Acad. Sci. USA* **99(6)**:5515-5520; Yu J-Y, DeRuiter SL, and Turner DL. (2002). RNA interference by expression of short-interfering RNAs and hairpin RNAs in mammalian cells. *Proc. Natl. Acad. Sci. USA* **99(9)**:6047-6052.

[22] Antisense or RNA interference molecules can be delivered *in vitro* to cells or *in vivo, e.g.,* to tumors of a mammal. Typical delivery means known in the art can be used. For example, delivery to a tumor can be accomplished by intratumoral injections. Other modes of delivery can be used without limitation, including: intravenous, intramuscular, intraperitoneal, intraarterial, local delivery during surgery, endoscopic, subcutaneous, and *per os.* In a mouse model, the antisense or RNA interference can be adminstered to a tumor cell *in vitro*, and the tumor cell can be subsequently administered to a mouse. Vectors can be selected for desirable properties for any particular application. Vectors can be viral or plasmid. Adenoviral vectors are useful in this regard. Tissue-specific, cell-type specific, or otherwise regulatable promoters can be used to control the transcription of the inhibitory polynucleotide molecules. Non-viral carriers such as liposomes or nanospheres can also be used.

[23] Using the p110α protein according to the invention, one of ordinary skill in the art can readily generate antibodies which specifically bind to the proteins. Such antibodies can be monoclonal or polyclonal. They can be chimeric, humanized, or totally human. Any functional fragment or derivative of an

antibody can be used including Fab, Fab', Fab2, Fab'2, and single chain variable regions. So long as the fragment or derivative retains specificity of binding for the endothelial marker protein it can be used. Antibodies can be tested for specificity of binding by comparing binding to appropriate antigen to binding to irrelevant antigen or antigen mixture under a given set of conditions. If the antibody binds to the appropriate antigen at least 2, 5, 7, and preferably 10 times more than to irrelevant antigen or antigen mixture then it is considered to be specific.

[24] Techniques for making such partially to fully human antibodies are known in the art and any such techniques can be used. According to one particularly preferred embodiment, fully human antibody sequences are made in a transgenic mouse which has been engineered to express human heavy and light chain antibody genes. Multiple strains of such transgenic mice have been made which can produce different classes of antibodies. B cells from transgenic mice which are producing a desirable antibody can be fused to make hybridoma cell lines for continuous production of the desired antibody. See for example, Nina D. Russel, Jose R. F. Corvalan, Michael L. Gallo, C. Geoffrey Davis, Liise-Anne Pirofski. Production of Protective Human Antipneumococcal Antibodies by Transgenic Mice with Human Immunoglobulin Loci *Infection and Immunity* April 2000, p. 1820-1826; Michael L. Gallo, Vladimir E. Ivanov, Aya Jakobovits, and C. Geoffrey Davis. The human immunoglobulin loci introduced into mice: V (D) and J gene segment usage similar to that of adult humans *European Journal of Immunology* 30: 534-540, 2000; Larry L. Green. Antibody engineering via genetic engineering of the mouse: XenoMouse strains are a vehicle for the facile generation of therapeutic human monoclonal antibodies *Journal of Immunological Methods 231* 11-23, 1999; Yang X-D, Corvalan JRF, Wang P, Roy CM-N and Davis CG. Fully Human Anti-interleukin-8 Monoclonal Antibodies: Potential Therapeutics for the Treatment of Inflammatory Disease States. *Journal of Leukocyte Biology* Vol. 66, pp401-410 (1999); Yang X-D,

Jia X-C, Corvalan JRF, Wang P, CG Davis and Jakobovits A. Eradication of Established Tumors by a Fully Human Monoclonal Antibody to the Epidermal Growth Factor Receptor without Concomitant Chemotherapy. *Cancer Research* Vol. 59, Number 6, pp1236-1243 (1999) ; Jakobovits A. Production and selection of antigen-specific fully human monoclonal antibodies from mice engineered with human Ig loci. *Advanced Drug Delivery Reviews* Vol. 31, pp: 33-42 (1998); Green L and Jakobovits A. Regulation of B cell development by variable gene complexity in mice reconstituted with human immunoglobulin yeast artificial chromosomes. *J. Exp. Med.* Vol. 188, Number 3, pp: 483-495 (1998); Jakobovits A. The long-awaited magic bullets: therapeutic human monoclonal antibodies from transgenic mice. *Exp. Opin. Invest. Drugs* Vol. 7(4), pp : 607-614 (1998) ; Tsuda H, Maynard-Currie K, Reid L, Yoshida T, Edamura K, Maeda N, Smithies O, Jakobovits A. Inactivation of Mouse HPRT locus by a 203-bp retrotransposon insertion and a 55-kb gene-targeted deletion: establishment of new HPRT-Deficient mouse embryonic stem cell lines. *Genomics* Vol. 42, pp: 413-421 (1997) ; Sherman-Gold, R. Monoclonal Antibodies: The Evolution from '80s Magic Bullets To Mature, Mainstream Applications as Clinical Therapeutics. *Genetic Engineering* News Vol. 17, Number 14 (August 1997); Mendez M, Green L, Corvalan J, Jia X-C, Maynard-Currie C, Yang X-d, Gallo M, Louie D, Lee D, Erickson K, Luna J, Roy C, Abderrahim H, Kirschenbaum F, Noguchi M, Smith D, Fukushima A, Hales J, Finer M, Davis C, Zsebo K, Jakobovits A. Functional transplant of megabase human immunoglobulin loci recapitulates human antibody response in mice. *Nature Genetics* Vol. 15, pp: 146-156 (1997); Jakobovits A. Mice engineered with human immunoglobulin YACs: A new technology for production of fully human antibodies for autoimmunity therapy. *Weir's Handbook of Experimental Immunology, The Integrated Immune System* Vol. IV, pp: 194.1-194.7 (1996) ; Jakobovits A. Production of fully human antibodies by transgenic mice. *Current Opinion in Biotechnology* Vol. 6, No. 5, pp: 561-566 (1995) ; Mendez M, Abderrahim H, Noguchi M, David N, Hardy M, Green L, Tsuda H, Yoast S, Maynard-Currie C, Garza D,

Gemmill R, Jakobovits A, Klapholz S. Analysis of the structural integrity of YACs comprising human immunoglobulin genes in yeast and in embryonic stem cells. *Genomics* Vol. 26, pp: 294-307 (1995); Jakobovits A. YAC Vectors: Humanizing the mouse genome. *Current Biology* Vol. 4, No. 8, pp: 761-763 (1994); Arbones M, Ord D, Ley K, Ratech H, Maynard-Curry K, Otten G, Capon D, Tedder T. Lymphocyte homing and leukocyte rolling and migration are impaired in L-selectin-deficient mice. *Immunity* Vol. 1, No. 4, pp: 247-260 (1994); Green L, Hardy M, Maynard-Curry K, Tsuda H, Louie D, Mendez M, Abderrahim H, Noguchi M, Smith D, Zeng Y, et. al. Antigen-specific human monoclonal antibodies from mice engineered with human Ig heavy and light chain YACs. *Nature Genetics* Vol. 7, No. 1, pp: 13-21 (1994); Jakobovits A, Moore A, Green L, Vergara G, Maynard-Curry K, Austin H, Klapholz S. Germ-line transmission and expression of a human-derived yeast artificial chromosome. *Nature* Vol. 362, No. 6417, pp: 255-258 (1993) ; Jakobovits A, Vergara G, Kennedy J, Hales J, McGuinness R, Casentini-Borocz D, Brenner D, Otten G. Analysis of homozygous mutant chimeric mice: deletion of the immunoglobulin heavy-chain joining region blocks B-cell development and antibody production. *Proceedings of the National Academy of Sciences USA* Vol. 90, No. 6, pp: 2551-2555 (1993); Kucherlapati et al., U.S. 6,l075,181.

[25] Antibodies can also be made using phage display techniques. Such techniques can be used to isolate an initial antibody or to generate variants with altered specificity or avidity characteristics. Single chain Fv can also be used as is convenient. They can be made from vaccinated transgenic mice, if desired. Antibodies can be produced in cell culture, in phage, or in various animals, including but not limited to cows, rabbits, goats, mice, rats, hamsters, guinea pigs, sheep, dogs, cats, monkeys, chimpanzees, apes.

[26] Antibodies can be labeled with a detectable moiety such as a radioactive atom, a chromophore, a fluorophore, or the like. Such labeled antibodies can be used for diagnostic techniques, either *in vivo*, or in an isolated test sample.

Antibodies can also be conjugated, for example, to a pharmaceutical agent, such as chemotherapeutic drug or a toxin. They can be linked to a cytokine, to a ligand, to another antibody. Suitable agents for coupling to antibodies to achieve an anti-tumor effect include cytokines, such as interleukin 2 (IL-2) and Tumor Necrosis Factor (TNF); photosensitizers, for use in photodynamic therapy, including aluminum (III) phthalocyanine tetrasulfonate, hematoporphyrin, and phthalocyanine; radionuclides, such as iodine-131 (^{131}I), yttrium-90 (^{90}Y), bismuth-212 (^{212}Bi), bismuth-213 (^{213}Bi), technetium-99m (^{99m}Tc), rhenium-186 (^{186}Re), and rhenium-188 (^{188}Re); antibiotics, such as doxorubicin, adriamycin, daunorubicin, methotrexate, daunomycin, neocarzinostatin, and carboplatin; bacterial, plant, and other toxins, such as diphtheria toxin, pseudomonas exotoxin A, staphylococcal enterotoxin A, abrin-A toxin, ricin A (deglycosylated ricin A and native ricin A), TGF-alpha toxin, cytotoxin from chinese cobra (naja naja atra), and gelonin (a plant toxin); ribosome inactivating proteins from plants, bacteria and fungi, such as restrictocin (a ribosome inactivating protein produced by *Aspergillus restrictus*), saporin (a ribosome inactivating protein from *Saponaria officinalis*), and RNase; tyrosine kinase inhibitors; ly207702 (a difluorinated purine nucleoside); liposomes containing antitumor agents (*e.g.*, antisense oligonucleotides, plasmids which encode for toxins, methotrexate, etc.); and other antibodies or antibody fragments, such as F(ab).

[27] Those of skill in the art will readily understand and be able to make such antibody derivatives, as they are well known in the art. The antibodies may be cytotoxic on their own, or they may be used to deliver cytotoxic agents to particular locations in the body. The antibodies can be administered to individuals in need thereof as a form of passive immunization.

[28] Given the success of small molecule protein kinase inhibitors, one can develop specific or non-specific inhibitors of p110α for treatment of the large number of patients with these mutations or cancers generally. It is clearly possible to develop broad-spectrum PI3K inhibitors, as documented by studies of

LY294002 and wortmannin (*2, 21,22*). Our data suggest that the development of more specific inhibitors that target p110α but not other PI3Ks would be worthwhile.

[29] Candidate chemotherapeutic agents can be identified as agents which inhibit p110α activity or expression. Test compounds can be synthetic or naturally occurring. They can be previously identified to have physiological activity or not. Tests on candidate chemotherapeutic agents can be run in cell-free systems or in whole cells. p110α activity can be tested by any means known in the art. These include methods taught in references 2, 22 and in Truitt et al., *J. Exp. Med.*, 179, 1071-1076 (1994). Expression can be monitored by determining PI3KCA protein or mRNA. Antibody methods such as western blotting can be used to determine protein. Northern blotting can be used to measure mRNA. Other methods can be used without limitation. When testing for chemotherapeutic agents, the p110α used in the assay can be a wild-type or an activated form. The activated form may contain a substitution mutation selected from the group consisting of E542K, E545K, Q546K, and H1047R. Moreover, inhibitors can be tested to determine their specificity for either p110α or an activated form of p110α . Comparative tests can be run against similar enzymes including PIK3CB, PIK3CG, PIK3C2A, PIK3C2B, PIK3C2G, PIK3C3, A-TM, ATR, FRAP1, LAT1-3TM,SMG1, PRKDC, and TRRAP to determine the relative specificity for the p110α enzyme.

[30] Once a non-synonymous, intragenic mutation in a PIK3CA coding sequence is identified in a test tissue of a patient, that information can be used to make therapeutic decisions. Patients with such mutations are good candidates for therapy with a p110α inhibitor. Such inhibitors can be specific or general for the family of inhibitors. Such inhibitors include LY294002 and wortmannin. Such inhibitors further include molecules comprising an antibody binding region specific for p110α . Such molecules are discussed above.

[31] Sets of primers for amplifying and/or sequencing PIK3CA can be provided in kits or assembled from components. Useful sets include pairs of forward and reverse primers optionally teamed with sequencing primers. The forward primers are shown in SEQ ID NO: 6 to 158. The reverse primers are shown in SEQ ID NO: 159 to 310. The sequencing primers are shown in : SEQ ID NO: 311 to 461. Pairs or triplets or combinations of these pairs or triplets can be packaged and used together to amplify and/or sequence parts of the PIK3CA gene. Pairs can be packaged in single or divided containers. Instructions for using the primers according to the methods of the present invention can be provided in any medium which is convenient, including paper, electronic, or a world-wide web address.

[32] While the invention has been described with respect to specific examples including presently preferred modes of carrying out the invention, those skilled in the art will appreciate that there are numerous variations and permutations of the above described systems and techniques that fall within the spirit and scope of the invention as set forth in the appended claims.

EXAMPLES

Example 1—This example demonstrates that the PIK3CA gene is the predominant target of mutations in this gene family

[33] To evaluate whether PI3Ks is genetically implicated in tumorigenesis, we directly examined the DNA sequences of members of this gene family in colorectal cancers.

[34] PI3K catalytic subunits are divided into three major classes depending on their substrate specificity (*5*). Additionally, a set of more distantly related proteins, including members of the mTOR family, constitute a fourth class (*6*). We used Hidden Markov models to identify 15 human genes containing kinase domains related to those of known PI3Ks in the human genome (*7*). These

comprised seven PI3Ks, six members of the mTOR subfamily and two uncharacterized PI3K-like genes (Table 1).

Table 1. PI3K genes analyzed

Gene name	Celera Accession	Genbank Accession	Alternate names	Group*
PIK3CA	hCT1640694	NM_006218	p110-alpha	Class IA
PIK3CB	hCT7084	NM_006219	PIK3C1, p110-beta	Class IA
PIK3CD	hCT2292011	NM_005026	p110-delta	Class IA
PIK3CG	hCT7976	NM_002649	PI3CG, PI3K-gamma	Class IB
PIK3C2A	hCT2270768	NM_002645	CPK, PI3-K-C2A, PI3K-C2alpha	Class II
PIK3C2B	hCT7448	NM_002646	C2-PI3K, PI3K-C2beta	Class II
PIK3C2G	hCT1951422	NM_004570	PI3K-C2-gamma	Class II
PIK3C3	hCT13660	NM_002647	Vps34	Class III
ATM	hCT29277	NM_000051	AT1, ATA, ATC, ATD, ATE, ATDC	Class IV
ATR	hCT1951523	NM_001184	FRP1, SCKL, SCKL1	Class IV
FRAP1	hCT2292935	NM_004958	FRAP, MTOR, FRAP2, RAFT1, RAPT1	Class IV
SMG1	hCT2273636	NM_014006	ATX, LIP, KIAA0421	Class IV
PRKDC	hCT2257127	NM_006904	p350, DNAPK, DNPK1, HYRC1, XRCC7	Class IV
TRRAP	hCT32594	NM_003496	TR-AP, PAF400	Class IV
none	hCT2257641	none		Class IV
none	hCT13051	none		Class IV

*PI3K genes are grouped into previously described classes (S3,S4). Class I, II and III comprise PI3K catalytic subunits, while class IV comprises PI3K-like genes including members of the mTOR (target of rapamycin), ATM (ataxia telangiectasia mutated), and DNAPK (DNA-dependent protein kinase) subfamilies, as well as two previously uncharacterized genes.

[35] We initially examined 111 exons encoding the predicted kinase domains of these genes (Table 2). The exons were polymerase chain reaction (PCR) amplified and directly sequenced from genomic DNA of 35 colorectal cancers (*8*). Only one of the genes (PIK3CA) contained any somatic (*i.e.*, tumor-specific) mutations.

Table 2. Primers used for PCR amplification and sequencing

Gene and Exon Name	Forward Primer[1]	Reverse Primer[2]	Sequencing Primer[3]
hCT2270768-Ex21	TTCCAGCCTGGGTAACAAAG	CGTCAGAACAAGACCCTGTG	AAAGGGGAAATGCGTAGGAC
hCT2270768-Ex22	CCTGACCTCAGGTGTTCTGC	CCCGGCCACTAAGTTATTTTTC	TCCCAAAGTGCTGGGATTAC
hCT2270768-Ex23	TGCACATTCTGCACGTGTATC	CTGCCATTAAATGCGTCTTG	CCAGAACTTAAAGTGAAATTTAAAAAG
hCT2270768-Ex24	TCCCAGTTTGTATGCTATTGAGAG	CTTTGGGCCTTTTTCATTCC	GCGAGGCAAAACACAAAGC
hCT2270768-Ex25	TGGAAATTCAAAAGTGTGTGG	TGTCTGGCTTATTTCACACG	TTGGAAATGGCTGTACCTCAG
hCT2270768-Ex26	CACTAATGAACCCCTCAAGACTG	AACTTTTGACAGCCTACTATGTGC	TACTTGAGCAGCCCACAGG
hCT2270768-Ex 27- 1	TCCTTGGCAAAGTGACAATC	GACCATTCATGAAAGAAACAAGC	AAAGGAATGAAAGTGGTTTTTGTC
hCT13660-Ex16	CTCTCACATACAACACCATCTCC	CCATGTACCGGTAACAAAAGAAG	TGCAATGTAATAGTTTTCCAAGG
hCT13660-Ex17	ATGTATCTCATTGAAAACCCAAC	TGAGCTTTCTAGGATCGTACCTG	CAGCAAATGAACTAAGCCACAG
hCT13660-Ex18	TCCCAAAGTGCTGGGATTAC	GCAGGAAGGTCCAACTTGTC	TGCTATACTATTTGCCCACAAAAC
hCT13660-Ex19	CCTATGACATAAATGCCAGTACAAAC	ATCTTCAACTGCGAACATGC	GAATGCATTTATTCAGAGATGAGG
hCT13660-Ex20	TCTTTTGTTCAGTCAGCATCTCTC	AAGCATCAATGACTACTTTAATCAAC	TGCTAGACACTTGCTGGTCAC
hCT13660-Ex21	TTGAGAATTCAGATGAGAAACCAG	TCCCAAAGTGCTGGGATTAC	TTGATATTAAAGTTGCACAAACTGC
hCT13660-Ex22	GAAGGCCACTCTCAAACCTG	TTGTTGCCTTTGTCATTTTG	TCAATTGTGTGACATATCACCTACC
hCT13660-Ex23	TCAAGGCTTGCATTTCATTG	ATGTGACTGTGGGCAGGAAC	TCACTGTAGAAATCCAAGTACCAC
hCT13660-Ex24	TTCCACACTCCAAAGAATGC	GCTGGTGAGATGTCAAAACG	TCTGCATCAGTTTGATTCTGC
hCT13660-Ex 25- 1	AATTGCAATCCTCTTGGTAGC	TCAACATATTACTTCCTCCAGAACTC	AATGCACTTTTTATTTTATTAG
hCT32594-Ex 66- 2	GCCAAGACCAAGCAACTCC	TTCTCCCATGTCAGGGAATC	GAAAAGTGCCGGTTCTTGAG
hCT32594-Ex 67- 1	ATAAACGACCGCTGGCCTAC	GACCCTCAAAGGCTAACGTG	GCCTACACAGTCCGTTTTCC
hCT32594-Ex 67- 2	GTACATCCGGGGACACAATG	TCCCTGGTCAGCACAGACTAC	AGAGGAGCGTGTGTTGCAG
hCT32594-Ex68	ACCGGGTTCTTCCAGCTAAG	AGCTGTCTCATTTCCACCATC	ACTCTGACGGTGGAGCTGAG
hCT32594-Ex 69- 1	CAATGCGTGCGTTAAATCTG	CGCGTCGTTTATGTCAAATC	GCTCTTGGTGCTAAGTTAAAGAGG

Table 2. Primers used for PCR amplification and sequencing

hCT32594-Ex 69- 2	CCCAATGCCACGGACTAC	CGCGTCGTTTATGTCAAATC	ATCCAGCTGGCTCTGATAGG
hCT32594-Ex70	ATCCAGCTGGCTCTGATAGG	CATAACACACAGGGGTGCTG	TGAACAGCCAGATCCTCTCC
hCT32594-Ex71	CTGGTGCTGAAACTCGACTG	GAACTGGGCGAGGTTGTG	GTCCCACCTTGTTAGGAAGC
hCT32594-Ex 72- 1	GTCTCGTTCTCTCCCTCACG	TCCCTTTCTTACACGCAAAC	TGGCATTCTGAAAACGGTTC
hCT32594-Ex 72- 2	CACAACCTCGCCCAGTTC	CAGTTCCGCCTGTACATTCAC	GCAAACAGCCTGGACAATC
hCT7976-Ex5	AGCATCACCCTCAGAGCATAC	AGCGCTCCTGCTTTCAGTC	CACATATTTCTGTCCCCTGTTG
hCT7976-Ex6	TGCCATACCTCTTAGGCACTTC	GTCTTGGCGCAGATCATCAC	TGTGGTTCTTTGGAGCACAG
hCT7976-Ex7	CGACAGAGCAAGATTCCATC	TTTTGTCACCAGTTGAAATGC	CCAAGGTACATTTCGGAAAAC
hCT7976-Ex8	AGATTGCCATCTGAGGAAGG	GACTGGGAAAAAGCATGAGC	ACCAGCCCTTTCCTCTTGTC
hCT7976-Ex9	GCATGGAGAGGAAGTGAACC	CGGTGATCATAATATTGTCATTGTG	TTCTTCCTCATGCCATTGTG
hCT7976-Ex10	TGGCCAGAGAGTTTGATTTATG	GGAAGTGTGGGCTTGTCTTC	GTGGCATCTGGCTGTCATC
hCT7976-Ex 11- 1	CCCTCAATCTCTTGGGAAAG	TGCACAGTCCATCCTTTGTC	CAATTAGTTTTCCTTGAGCACTCC
hCT7976-Ex 11- 2	TGGTTTCTTCTCATGGACAGG	AATGCCAGCTTTCACAATGTC	TCTTCTTTATCCAGGACATCTGTG
hCT7448-Ex21	GGGTGTCCACACTTCTCAGG	GGCCAAGACCACATGGTAAG	CCTGGGAGAGGTCTGGTTC
hCT7448-Ex22	CCGGAAGAAACAATGAGCAG	TCCTACATTAAGACAGCATGGAAC	GGCAGCATCTTGGTCTGAAG
hCT7448-Ex23	GGTGTGAGCTGAGTGAGCAG	TGCCTCCCTTTTAAGGCTATC	GAGCACTTGGGAGACCTGAG
hCT7448-Ex24	GTGGGAATGACCTTCCTTTC	AGGTCCTTCTGCCAACAAAG	AGGGAAGCATGAGCACAGTC
hCT7448-Ex25	GGATGAACAGGCAGATGTGAG	CGTCTTCTCTCCTCCAATGC	TGAGTTCTGTCTGGCTGTGG
hCT7448-Ex26	AGCCCCTTCTATCCAGTGTG	GGTATTCAGTTGGGGCTCAG	TGATGAGGGATGAGGGAAAC
hCT7448-Ex27	TGCCCACAGCATCTGTCTAC	TGTATCCACGTGGTCAGCTC	AGGGTTAGGGAGCCTAGCTG
hCT7448-Ex 28- 1	ATTGTGTGCCAGTCATTTGC	ACAGGACGCTCGGTCAAC	TCCTTGGAACACCCCTGTC
hCT1951523-Ex 39- 2	TTCCACATTAAGCATGAGCAC	TTGCCATCAGTACAAATGAGTTTAG	CAGTCATGATACCTACACTTCCATC
hCT1951523-Ex40	GACAGTCATTCTTTTCATAGGTCATAG	TTCCTGCTTTTTAAGAGTGATCTG	CAACTCTGAAATAAAAGCAATCTGG
hCT1951523-Ex41	CCACATAGTAAGCCTTCAATGAC	AGGAAGGAAGGGATGGAAAC	TTCTTTGGTTATGAAATGAACAATC
hCT1951523-Ex42	TGAAAAATGTTCCTTTATTCTTG	AGAAACCACTCATGAAAA	TTGAATAAAAGTAGATGTTTCTTGTCC
hCT1951523-Ex43	TCTGAGAACATTCCCTGATCC	CGCATTACTACATGATCCACTG	TACCAAGAATATAATACGTTGTTATGG
hCT2257127-Ex76	TCAGCTCTCTAATCCTGAACTGC	TGTCACAGAAAGCATGAGACC	CGGCTTCTGGCACATAAAAC
hCT2257127-Ex 77- 1	AGCAGAGAAGAAACATATACCAT	AGAAATAACTGTCAATATCCCAGTATCAC	CCATTGAGCACTCCATTCATTAC
hCT2257127-Ex 77- 2	CATTTTGGGAAAGGAGGTTC	TCATTAAACATTTAGTAATGTGTGCTC	CCCTGGGAATCTGAAAGAATG

Table 2. Primers used for PCR amplification and sequencing

hCT2257127-Ex78	ATTACAGGCGTGAGCCACTG	AGGCAACAGGGCAAGACTC	TGGGCCGTTGTCTCATATAC
hCT2257127-Ex 79- 1	TTTGGCACTGTCTTCAGAGG	CCTGAAAGGGAGAATAAAAGG	CACTCTGGCTTTTCCCTCTG
hCT2257127-Ex 79- 2	AGAGGGAACACCCTTTCCTG	CCTGAAAGGGAGAATAAAAGG	AGGTCATGAATGGGATCCTG
hCT2257127-Ex80	TATAGCGTTGTGCCCATGAC	TATTGACCCAGCCAGCAGAC	CATATTGCTTGGCGTCCAC
hCT2257127-Ex81	TCCTGCCTCTTTGCTATTTTTCAATG	TATATTGAGACTCAAATATCGA	TCTTGGTGATCTTTGCCTTTG
hCT2257127-Ex82	TTGCCTCAGAGAGATCATCAAG	TGATGCATATCAGAGCGTGAG	TCATCAAGATTATTCGATATTTGAGTC
hCT2257127-Ex 83- 1	TAGGGGCGCTAATCGTACTG	TTCAATGACCATGACAAAACG	CGAGAAAGTAAAGTGCCTGCTG
hCT2257127-Ex 83- 2	TCTGATATGCATCAGCCACTG	TTCAATGACCATGACAAAACG	CGGGATTGGAGACAGACATC
hCT2257127-Ex84	TGATTTCAAGGGAAGCAGAG	TGGTTTTCAAGCAGACAATCC	GAGGATGCTGCCATTTGTG
hCT2257127-Ex85	TGTAGAAAGCAAGGCTGCTC	TCCTCCTCAATGAAAGCAGAG	CATGCTAACAGAGTGTCAAGAGC
hCT1951422-Ex19	ACCCCAAAGTCATCCAAGTG	CAATGTGATCCCAACTGGTC	CGAATTCTTTTTGCCATTTC
hCT1951422-Ex20	AAAGGCTCCAGTTGATGGAC	TTATTGCCAATTGGAGTTTGG	AAAGTCTGCAAGGGGCTATG
hCT1951422-Ex21	CCATTAAAACCACTCTAAGTCAGG	TTCTGTTGGCTTATCATTTTTG	TCAGGCTAGAAATGTATCCAAGG
hCT1951422-Ex22	AAGCCTCCTCCAGAAAAGAAG	CCCAGAAACTAAATAAAATGCAG	AAAGGAAAGGGGTAATCCAG
hCT1951422-Ex23	CCCTCCTGTCCACTGAGATG	AATCAAATTTGTTGCATTAAAAATC	TTTACTTTTTATGATTACCTCTGATGC
hCT1951422-Ex24	TCTCAAGCTGCCTCACAATG	GTTTTCTCATTCCTTTCTCTTCC	AAAGAAAATTCAAATGAAAATAAGTCG
hCT1951422-Ex25	AAAGACATTGCCATGCAAAC	TTTGGGAAAGGGAACACAAG	CATGCAAACTTGGGTCTAGATG
hCT1951422-Ex26	TTGTTGGGCTCCAAATAAAC	GATTTTTCCTTGGAACATCCTC	TTGGCTTTTTCCCCTCATAC
hCT13051-Ex5	CCCTGGAGTGCTTACATGAG	CGGGGATCAGATTTGCTATG	TAAAGCCTTTCCCAGCTCAG
hCT13051-Ex6	GACTTTATAAACACTCGACATTAGAGC	TAGGGGGTCATCCTCAGGTC	CCTGCTGCTTCCACAGGAC
hCT13051-Ex7	ATGATGACCTCTGGCAGGAC	GTCTTCCCCTGCTCAATCAC	CATGGACGTCCTGTGGAAG
hCT13051-Ex8	GAATCAACCGTCAGCGTGTC	GACACGTTGTGGGCCAGCCAGT	GTGTCCCATTCATCCTCACC
hCT13051-Ex9	CTGGCACCGGGGAAAACAGAG	CTGCCGGTTATCTTCGGACACGTT	AACAGAGGAGGCGCTGAAG
hCT2282983-Ex40	TGGACATCGACTACAAGTCTGG	TGAGTGAGGGCAGACAGATG	GCCTCACCCTACCCATCC
hCT2282983-Ex41	TCCTTGGGGTTTTGAAGAAG	TGGCACCTGAACCATGTAAG	AGATTGCTGGGGTTCCTTTC
hCT2282983-Ex42	AAGGCCTTCCAGACTCTTGC	CGTACATGCCGAAGTCTGTC	CCACCTCACTCCATCTCTGG
hCT2282983-Ex43	CCTCTTTGTTTTTCCCTACCG	GCCCTGGTTTTAACCCTTAAC	TGGGGTAAGTTCCCTGAGTG
hCT2282983-Ex 44- 1	CTTCCACAGTGGGGGTACAG	CCAGCTCCAGCTTCTGACTC	TACAGAGCCAGGGAGAGTGC
hCT2282983-Ex 44- 2	_GACACAACGGCAACATTATGCTG	TTGTGTTTTCTTGGAGACAG	TATCATCCACATCGGTCAGC

Table 2. Primers used for PCR amplification and sequencing

hCT2292935-Ex46	CATTCCAAAGCATCTGGTTTTAC	CAATGAGCATGGGAGAGATG	TTTGGGACAAGTAATTGTTATTAGC
hCT2292935-Ex47	TTGTGAGGAACGTGTGATTAGG	TGGAGTTTCTGGGACTACAGG	TTGAATGCAGTGGTGCTCTC
hCT2292935-Ex48	CTGGGCAACAGAGCAAGAC	CCTTCTTCAAAGCTGATTCTCTC	TCTGCCTGTGTTCTGAGCTG
hCT2292935-Ex49	TCCCTTCTCCTTTGGCTATG	CGCTCTACAGCCAATCACAG	GAACTCAGCTCTGCCTGGAC
hCT2292935-Ex50	ATAGCACCACTGCCTTCCAG	TGGCATCACAATCAATAGGG	GCGAGACTCGGTCTCAAAAG
hCT2292935-Ex51	TGCAGAAGTGGAGGTGGAG	CTCCAAGGGGGTTAGAGTCC	ATCGTTTGCCAACTCCTAGC
hCT2292935-Ex52	AACCCAAGCTGCTTCCTTTC	CAGGAAACCAGGTCAGAAGTG	AATCAGTGCAGGTGATGCAG
hCT2292935-Ex53	AGTCCTGCCCTGATTCCTTC	TTTTTGCAGAAAGGGGTCTTAC	ACATGGCCTGTGTCTGCTTC
hCT2292935-Ex54	CCCACCCACTTATTCCTGAG	GCCCACCCCACTCTAGAAAC	GACTGGAAGAAAATAACCAAGTTTC
hCT2292935-Ex55	TTTCCCCTTTAGGGTAGGTAGG	TGGAACCTTTTCTGCTCAAAG	GGCAGGCGTTAAAGGAATAG
hCT2292935-Ex56	CGGACATAGAGGAAGGATTGC	AGCTGCATGGTGCCAAAG	AAAAACAGGGCACCCATTG
hCT2292935-Ex57	TGGCCAAACTTTTCAAATCC	ATAACAATGGGCACATGCAG	TTAAGCCCACAGGGAACAAG
hCT2292935-Ex 58- 1	TGGGAGAGCTCAGGGAATAC	GGTCATTCTTCCATCAGCAAG	TGTCAGACCTTGGCCTTTTC
hCT2273636-Ex 35- 1	TCCCAAAGTGCTGGGATTAC	CACACCCACACTCACACAAAG	TCTTCTGAAAAATGGAGGAAGTC
hCT2273636-Ex 35- 2	TTGGCTGCCATGACTAACAC	GGCACTGCAGGCTAATAATG	GCTCTTCCTGGGGAAGTCTC
hCT2273636-Ex 36- 1	GCTCTCAGTGTGCCTCATGG	GGGACCTCAAGTCTTTTCCTTC	CAGTTTTTGACTGCCACTGC
hCT2273636-Ex 36- 2	AAGAAACACCCCGGTTCC	GGGACCTCAAGTCTTTTCCTTC	TCCATGCTCGACACTATTCTG
hCT2273636-Ex 37- 1	AAATTTAGTTGAGTAATGAGAGAATGC	GGAAGGGAAGGAGGACAAAC	TTCTACTTTACATACAAAAGGCACTC
hCT2273636-Ex 37- 2	GTAAAATTGGCCCTGCTTTG	CGTCTCAAACTACCAAGTCTGG	AGTTGGGCTTAGCCTGGATG
hCT2273636-Ex38	CATAACCACATGCAGCAACC	CACCCAGTGCTGTTTCAATG	AGTATCACGTCCATGTTGGAG
hCT2273636-Ex39	AATTGGCCTTGGAGACAGAC	CGCCGCATAATGTGTAAAAC	CAATGTTTGCTTTGAAAAAGG
hCT2273636-Ex 40- 1	TTCATGTGAGCAGGTATGCTG	TGCCATATTTAACTGCCATTTC	TGAGCAAAACCTGTGGAATG
hCT2273636-Ex 40- 2	TTGTGTACGACCCTCTGGTG	TGCCATATTTAACTGCCATTTC	TTTGCTGGTGCTGTCTATGG
hCT2273636-Ex41	TTTGTACAGTGGAGGCAACG	GCAGTCACTGAGACAGCTTTTATC	GGATGTGCAAAATGTTCTTCTG
hCT7084-Ex17	CAGCTGGTTATGTGTGTTTATGG	TAAGCATAGCCTCGGAGAAC	GGGAGCAGGTGTTATTGATTG
hCT7084-Ex18	TGTCCTCATGGTTGCTTTTC	GGACCATTAATAGCTACCTTCCTG	GGTGAGGAGTTTTCCCAAGC
hCT7084-Ex19	CAGGGACATGCTATCCAAAG	AGGCAAGACAACATATTTGAAAG	AGCACAGAGTTTGTTAATGTTTTTAG
hCT7084-Ex20	TGGTGGAACTTGTGTTTTTCC	AAGGGCTATGTGTCATTTTGTTC	GCTGACTTCTATTGGGAGCATAC
hCT7084-Ex21	TCATACGGTTTTGGCAGCTC	CATCAAGCAAGCAAACAAATG	CAGAGGTATGGTTTGGGTCTC

Table 2. Primers used for PCR amplification and sequencing

hCT7084-Ex22	ACAGAGGGAGAAGGGCTCAG	AATTCCCCCAAAAGCTTCC	TGGGGGTCTAGGACTATGGAG
hCT7084-Ex23	TGGGACAATTTTCGGCAGAAG	TTCCCTCCTGGCTAAGAACC	GCTGTGTTTTCTTAATTTCCTGTATG
hCT7084-Ex 24- 1	ATGAAGCATGCTGCCTGATG	AAAAGCAGAGGGAATCATCG	CAGCCTCCTGCAGACTTTG
hCT2257641-Ex 1- 56	GGGGGCCTTAGAAGGAAG	TCCCATTCATGACCTGGAAG	CATTTTGGGAAAGGAGGTTC
hCT2257641-Ex 1- 57	TGGAGTTCCTGAGAAATGAGC	GGCCCGCTTTAAGAGATCAG	CGGTCAGTATGACGGTAGGG
hCT2257641-Ex 1- 58	AGAGGGAACACCCTTTCCTG	CATGCCCAAAGTCGATCC	AGGTCATGAATGGGATCCTG
hCT2257641-Ex 1- 59	CATGATGTTGGAGCTTACATGC	ACACATCCATGGTGTTGGTG	GGCGCTAATCGTACTGAAAC
hCT2257641-Ex 1- 60	CGGGATTGGAGACAGACATC	TGCCACAGCCACATAGTCTC	TATGGTGGCCATGGAGACTG
hCT2257641-Ex 1- 61	CATCATGGTACACGCACTCC	TTCTATCTGCAGACTCCCACAG	AGGAGCCCTCCTTTGATTG
hCT29277-Ex55	CTCAATCAGAGCCTGAACCAC	GGAAAAGAAAGCAGGAGAAGC	GGCCAGTGGTATCTGCTGAC
hCT29277-Ex56	CCCGGCCTAAAGTTGTAGTTC	AAATGGAGAAAAGCCTGGTTC	AAGACAAAATCCCAAATAAAGCAG
hCT29277-Ex57	TGGGAGACTGTCAAGAGGTG	AAGCAATCCTCCCACCTTG	ATTGGTTTGAGTGCCCTTTG
hCT29277-Ex58	TTCCTCCAAGGAGCTTTGTC	CCTTCCTTTTTCACTCACACAC	AAAATGCTTTGCACTGACTCTG
hCT29277-Ex59	TTCCCTGTCCAGACTGTTAGC	TGATTTAATAATGAAGATGGGTTGG	TTCATCTTTATTGCCCCTATATCTG
hCT29277-Ex60	CCGGTTATGCACATCATTTAAG	ACTCAGTACCCCAGGCAGAG	TTAAAGATTATACCAAGTCAGTGGTC
hCT29277-Ex61	GCAGCCAGAGCAGAAGTAAAC	TCAAACTCCTGGGCTCAAAC	CATGTGGTTTCTTGCCTTTG
hCT29277-Ex62	TCTAATGAAAGCCCACTCTGC	CAGCCACATCCCCCTATG	AAGCATAGGCTCAGCATACTACAC
hCT29277-Ex63	AAGTGTGCATGATGTTTGTTCC	TGCCTTCTTCCACTCCTTTC	CCCATCAACTACCATGTGACTG
hCT29277-Ex 64- 1	GATGACCAAGAATGCAAACG	AAGAGTGAAAGCAGAGATGTTCC	GGTCCTGTTGTCAGTTTTTCAG
NM_005026 Ex17	ATCATCTTTAAGAACGGGGATGG	ACTAAGCCTCAGGAGCAGCCT	GGTCCTGGGGTGCTCCTAGA
NM_005026 Ex18	CCTCAGATGCTGGTGCCG	GATACTTGGGGAAGAGAGACCTACC	TCCTCAACTGAGCCAAGTAGCC
NM_005026 Ex19	TCTTCATGCCTTGGCTCTGG	GAGGGGAGAGGAGGGGGAG	TGTGTCCTCCATGTTCTGTTGG
NM_005026 Ex20	TCCGAGAGAGTGGGCAGGTA	CACAAACCTGCCCACATTGC	TGGCCCCTCTGCCTAGCA
NM_005026 Ex21	GGGCAGGTTTGTGGGTCAT	CCTGGGCGGCTCAACTCT	CCACTGCTGGGTCCTGGG
NM_005026 Ex22	GGAACTGGGGGCTCTGGG	AGGCGTTTCCGTTTATGGC	GAATAGAGAGCTTTTCCTGAGATGC
hCT1640694-Ex 1- 1	GTTTCTGCTTTGGGACAACCAT	CTGCTTCTTGAGTAACACTTACG	GATTCATCTTGAAGAAGTTGATGG
hCT1640694-Ex 1- 2	CTCCACGACCATCATCAGG	GATTACGAAGGTATTGGTTTAGACAG	ACTTGATGCCCCCAAGAATC
hCT1640694-Ex 1- 3	CCCCCTCCATCAACTTCTTC	GGTGTTAAAAATAGTTCCATAGTTCG	CTCAAGAAGCAGAAAGGGAAG
hCT1640694-Ex 2- 1	TCATCAAAAATTTGTTTTAACCTAGC	TATAAGCAGTCCCTGCCTTC	TCTACAGAGTTCCCTGTTTGC

Table 2. Primers used for PCR amplification and sequencing

hCT1640694-Ex 2- 2	TTCTGAACGTTTGTAAAGAAGCTG	TATAAGCAGTCCCTGCCTTC	GCTGTGGATCTTAGGGACCTC
hCT1640694-Ex 3- 1	GCAGCCCGCTCAGATATAAAC	CTGGGCGAGAGTGAGATTCC	AAAAAGCATTTCTGATATGGATAAAG
hCT1640694-Ex 3- 2	TCTGAAAATCAACCATGACTGTG	ATGAACCCAGGAGGCAGAG	TCGAAGTATGTTGCTATCCTCTG
hCT1640694-Ex 4- 1	TCTTGTGCTTCAACGTAAATCC	CGGAGATTTGGATGTTCTCC	AAAATAATAAGCATCAGCATTTGAC
hCT1640694-Ex 4- 2	TCTCAACTGCCAATGGACTG	CGGAGATTTGGATGTTCTCC	TTATTCCAGACGCATTTCCAC
hCT1640694-Ex5	TAGTGGATGAAGGCAGCAAC	TTTGTAGAAATGGGGTCTTGC	TTTGAGTCTATCGAGTGTGTGC
hCT1640694-Ex6	TGCCTTTTCCAATCAATCTC	AATTCCTGAAGCTCTCCCAAG	TTCCTGTTTTTCGTTTGGTTG
hCT1640694-Ex7	GGGGAAAAAGGAAAGAATGG	TGCTGAACCAGTCAAACTCC	TGAATTTTCCTTTTGGGGAAG
hCT1640694-Ex8	TTTGCTGAACCCTATTGGTG	TTGCAATATTGGTCCTAGAGTTC	TGGATCAAATCCAAATAAAGTAAGG
hCT1640694-Ex9	GATTGGTTCTTTCCTGTCTCTG	CCACAAATATCAATTTACAACCATTG	TTGCTTTTTCTGTAAATCATCTGTG
hCT1640694-Ex10	ACCTTTTGAACAGCATGCAA	TGGAAATAATGTTAAGGGTGTTTTT	TATTTCATTTATTTATGTGGAC
hCT1640694-Ex11	AAAACACCCTTAACATTATTTCCATAG	TCTGCATGGCCGATCTAAAG	GAAGTTAAGGCAGTGTTTTAGATGG
hCT1640694-Ex12	TTTATTCTAGATCCATACAACTTCCTTT	AAAGTTGAGAAGCTCATCACTGGTAC	ACCAGTAATATCCACTTTCTTTCTG
hCT1640694-Ex13	CTGAAACTCATGGTGGTTTTG	TGGTTCCAAATCCTAATCTGC	TTTATTGGATTTCAAAAATGAGTG
hCT1640694-Ex14	GAGTGTTGCTGCTCTGTGTTG	TTGAGGGTAGGAGAATGAGAGAG	TCTCATGTGAGAAAGAGATTAGCAG
hCT1640694-Ex15	GGATTCCTAAATAAAAATTGAGGTG	CATGCATATTTCAAAGGTCAAG	TGGCTTTCAGTAGTTTTCATGG
hCT1640694-Ex16	TTGCTTTCCTGAAGTTTCTTTTG	TCAAGTAAGAGGAGGATATGTCAAAG	CATGTGATGGCGTGATCC
hCT1640694-Ex17	GGGGAAAGGCAGTAAAGGTC	CATCAAATATTTCAAAGGTTGAGC	AGGAATACACAAACACCGACAG
hCT1640694-Ex18	TCCTTATTCGTTGTCAGTGATTG	GTCAAAACAAATGGCACACG	TGCACCCTGTTTTCTTTTCTC
hCT1640694-Ex19	CATGGTGAAAGACGATGGAC	TTACAGGCATGAACCACCAC	TGGACAAGTAATGGTTTTCTCTG
hCT1640694-Ex 20- 1	TGGGGTAAAGGGAATCAAAAG	CCTATGCAATCGGTCTTTGC	TGACATTTGAGCAAAGACCTG
hCT1640694-Ex 20- 2	TTGCATACATTCGAAAGACC	GGGGATTTTTGTTTTGTTTTG	TTTGTTTTGTTTTGTTTTTT

[1]SEQ ID NO: 6 to 165 (forward primers)
[2]SEQ ID NO: 166 to 325 (reverse primers)
[3]SEQ ID NO: 326 to 485 (sequencing primers)

Example 2—This example demonstrates the striking clustering of mutations within the PIK3CA gene

[36] All coding exons of PIK3CA were then analyzed in an additional 199 colorectal cancers, revealing mutations in a total of 74 tumors (32%) (Table 3 and examples in Figure 1).

Table 3 . *PIK3CA* mutations in human cancers

	PIK3CA mutations[a]			Tumor type[b]								
Exon	Nucleotide	Amino acid	Functional domain	Colon	GBM	Gastric	Breast	Lung	Pancreas	Medullo-blastomas	Adenomas	Total
Exon 1	C112T	R38C	p85	1								1
Exon 1	G113A	R38H	p85	2								2
Exon 1	G263A	R88Q	p85	1								1
Exon 1	C311G	P104R	p85	1								1
Exon 1	G317T	G106V	p85	1								1
Exon 1	G323C	R108P	p85	1								1
Exon 1	del332-334	delK111		1								1
Exon 2	G353A	G118D		1								1
Exon 2	G365A	G122D		1								1
Exon 2	C370A	P124T		1								1
Exon 4	T1035A	N345K	C2	1								1
Exon 4	G1048C	D350H	C2		1							1
Exon 5	T1132C	C378R	C2		1							1
Exon 7	T1258C	C420R	C2	2								2
Exon 7	G1357C	E453Q	C2	1								1
Exon 9	C1616G	P539R	Helical	1								1
Exon 9	G1624A	E542K	Helical	9							1	10
Exon 9	A1625G	E542G	Helical	1								1
Exon 9	A1625T	E542V	Helical								1	1
Exon 9	G1633A	E545K	Helical	21				1				22
Exon 9	A1634G	E545G	Helical	1								1
Exon 9	G1635T	E545D	Helical	1								1
Exon 9	C1636A	Q546K	Helical	5								5
Exon 9	A1637C	Q546P	Helical	1								1
Exon 12	C1981A	Q661K	Helical	1								1
Exon 13	A2102C	H701P	Helical		1							1
Exon 18	G2702T	C901F	Kinase	1		1						2
Exon 18	T2725C	F909L	Kinase	1								1
Exon 20	T3022C	S1008P	Kinase	1								1
Exon 20	A3073G	T1025A	Kinase	1								1
Exon 20	C3074A	T1025N	Kinase	1								1
Exon 20	G3129T	M1043I	Kinase	2								2
Exon 20	C3139T	H1047Y	Kinase	2								2
Exon 20	A3140G	H1047R	Kinase	15		2	1					18
Exon 20	A3140T	H1047L	Kinase	1								1
Exon 20	G3145A	G1049S	Kinase		1							1
Tumors with mutations				74	4	3	1	1	0	0	2	
No. samples screened				234	15	12	12	24	11	12	76	
Percent of tumors with mutations				32%	27%	25%	8%	4%	0%	0%	3%	

[a]Exon number with nucleotide and amino acid change resulting from mutation. Nucleotide position refers to position within coding sequence, where position 1 corresponds to the first position of the start codon. Functional domains are described in Fig. 1 legend. [b]Number of non-synonymous mutations observed in indicated tumors. Colon, colorectal cancers; GBM, glioblastomas; gastric, gastric cancers; breast, breast cancers; lung, lung cancers; pancreas, pancreatic cancers; medulloblastomas; adenomas, benign colorectal tumors. All mutations listed were shown to be somatic except for five colorectal cancers and one glioblastoma where no corresponding normal tissue was available. Mutations were identified in 96 of 201 mismatch repair (MMR) proficient colorectal cancers, and 16 of 33 MMR-deficient colorectal cancers. Some tumors with *PIK3CA* mutations contained mutations in *KRAS* or *BRAF* while others did not, suggesting that these genes operate through independent pathways. Seven tumors contained two somatic alterations. In addition to the 92 nonsynonymous mutations recorded in the table, we detected 3 synonymous alterations.

Example 3—This example demonstrates that the mutations in PIK3CA occur late in tumorigenesis.

[37] To determine the timing of PIK3CA mutations during neoplastic progression, we evaluated 76 pre-malignant colorectal tumors of various size and degree of dysplasia. Only two PIK3CA mutations were found (E542K and E542V), both in very advanced adenomas greater than 5 cm in diameter and of tubuluvillous type. These data suggest that PIK3CA abnormalities occur at relatively late stages of neoplasia, near the time that tumors begin to invade and metastasize.

Example 4—This example demonstrates that PIK3CA mutations in a variety of different cancer types.

[38] We then evaluated PIK3CA for genetic alterations in other tumor types (Table 1). Mutations were identified in four of fifteen (27%) glioblastomas, three of twelve (25%) gastric cancers, one of thirteen (8%) breast, and one of twenty four (4%) lung cancers. No mutations were observed in eleven pancreatic cancers or twelve medulloblastomas. In total, 89 mutations were observed, all but 3 of which were heterozygous.

Example 5—This example demonstrates the non-random nature of the genetic alterations observed.

[39] The sheer number of mutations observed in PIK3CA in five different cancer types strongly suggests that these mutations are functionally important. This conclusion is buttressed by two additional independent lines of evidence. First, analysis of the ratio of non-synonymous to synonymous mutations is a good measure of selection during tumor progression, as silent alterations are unlikely to exert a growth advantage. The ratio of non-synonymous to synonymous mutations in PIK3CA was 89 to 2, far higher than the 2:1 ratio expected by chance ($P<1x10^{-4}$). Second, the prevalence of non-synonymous changes located in the PI3K catalytic and accessory domains was ~120

per Mb tumor DNA, over 100 times higher than the background mutation frequency of nonfunctional alterations observed in the genome of cancer cells ($P<1x10^{-4}$) (*9*).

[40] Although the effect of these mutations on kinase function has not yet been experimentally tested, their positions and nature within PIK3CA imply that they are likely to be activating. No truncating mutations were observed and >75% of alterations occurred in two small clusters in exons 9 and 20 (Table 2 and Figure 1). The affected residues within these clusters are highly conserved evolutionarily, retaining identity in mouse, rat, and chicken. The clustering of somatic missense mutations in specific domains is similar to that observed for activating mutations in other oncogenes, such as RAS (*10*), BRAF (*11, 12*), β-catenin (*13*), and members of the tyrosine kinome (*14*).

[41] These genetic data suggest that mutant PIK3CA is likely to function as an oncogene in human cancers.

Example 6—This example demonstrates that gene amplification of PIK3CA is not common.

[42] Quantitative PCR analysis of PIK3CA in 96 colorectal cancers showed no evidence of gene amplification, suggesting that gene copy alterations are not a significant mechanism of activation in this tumor type. The primers used were:

Real time PI3K hCT1640694 20-1F (intron)

TTACTTATAGGTTTCAGGAGATGTGTT (SEQ ID NO: 486); and

Real time PI3K hCT1640694 20-1R

GGGTCTTTCGAATGTATGCAATG (SEQ ID NO: 487)

[43] The Sequence Listing appended to the end of this application contains the following sequences:

SEQ ID NO: 1=coding sequence only (nt 13 to 3201 of SEQ ID NO: 2)
SEQ ID NO: 2=mRNA sequence (NM_006218)
SEQ ID NO: 3=protein sequence (NP_006209)
SEQ ID NO: 4=exon 9
SEQ ID NO: 5=exon 20
SEQ ID NO: 6 to 165 =forward primers
SEQ ID NO: 166 to 325=reverse primers
SEQ ID NO: 326 to 485=sequencing primers
SEQ ID NO: 486 and 487 amplification primers

References and Notes

1. R. Katso *et al.*, *Annu Rev Cell Dev Biol* 17, 615-75 (2001).

2. I. Vivanco, C. L. Sawyers, *Nat Rev Cancer* 2, 489-501 (Jul, 2002).

3. W. A. Phillips, F. St Clair, A. D. Munday, R. J. Thomas, C. A. Mitchell, *Cancer* 83, 41-7 (Jul 1, 1998).

4. E. S. Gershtein, V. A. Shatskaya, V. D. Ermilova, N. E. Kushlinsky, M. A. Krasil'nikov, *Clin Chim Acta* 287, 59-67 (Sep, 1999).

5. B. Vanhaesebroeck, M. D. Waterfield, *Exp Cell Res* 253, 239-54 (Nov 25, 1999).

6. S. Djordjevic, P. C. Driscoll, *Trends Biochem Sci* 27, 426-32 (Aug, 2002).

7. Catalytic subunits of PI3Ks were identified by analysis of InterPro (IPR) PI3K domains (IPR000403) present within the Celera draft human genome sequence. This resulted in identification of 15 PI3Ks and related PI3K genes. The kinase domain of PIK3CD gene was not represented in the current draft of human genome sequence and was therefore not included in this study.

8. Sequences for all annotated exons and adjacent intronic sequences containing the kinase domain of identified PI3Ks were extracted from the Celera draft human genome sequence (URL address: www host server, domain name celera.com). Celera and Genbank accession numbers of all analyzed genes are available in Table 1. Primers for PCR amplification and sequencing were designed using the Primer 3 program (URL address: http file type, www-genome.wi.mit.edu host server, cgi-bin domain name, primer directory, primer3_www.cgi subdirectory), and were synthesized by MWG (High Point, NC) or IDT (Coralville, IA). PCR amplification and sequencing were performed on tumor DNA from early passage cell lines or primary tumors as previously described (*12*) using a 384 capillary automated sequencing apparatus (Spectrumedix, State College, PA). Sequence traces were assembled and analyzed to identify potential genomic alterations using the Mutation Explorer software package (SoftGenetics, State College, PA). Of the exons extracted, 96% were

successfully analyzed. Sequences of all primers used for PCR amplification and sequencing are provided in Table S1.

9. T. L. Wang *et al.*, *Proc Natl Acad Sci U S A* 99, 3076-80. (2002).

10. J. L. Bos *et al.*, *Nature* 327, 293-7 (1987).

11. H. Davies *et al.*, *Nature* (Jun 9, 2002).

12. H. Rajagopalan *et al.*, *Nature* 418, 934. (2002).

13. P. J. Morin *et al.*, *Science* 275, 1787-90 (1997).

14. A. Bardelli *et al.*, *Science* 300, 949 (May 9, 2003).

15. J. Li *et al.*, *Science* 275, 1943-7 (1997).

16. P. A. Steck *et al.*, *Nat Genet* 15, 356-62 (1997).

17. T. Maehama, J. E. Dixon, *J Biol Chem* 273, 13375-8 (May 29, 1998).

18. M. P. Myers *et al.*, *Proc Natl Acad Sci U S A* 95, 13513-8 (Nov 10, 1998).

19. L. Shayesteh *et al.*, *Nat Genet* 21, 99-102 (Jan, 1999).

20. J. Q. Cheng *et al.*, *Proc Natl Acad Sci U S A* 89, 9267-71 (Oct 1, 1992).

21. L. Hu, J. Hofmann, Y. Lu, G. B. Mills, R. B. Jaffe, *Cancer Res* 62, 1087-92 (Feb 15, 2002).

22. J. Luo, B. D. Manning, L. C. Cantley, Cancer Cell 4, 257-62 (2003).

We Claim:

1. A method of assessing cancer in a body sample of a human suspected of havng a cancer, comprising the steps of:

   determining a non-synonymous, intragenic mutation in a PIK3CA coding sequence in the body sample, wherein a wild-type PIK3CA coding sequence comprises the sequence shown in SEQ ID NO:2;

   identifying the human as likely to have cancer if a non-synonymous, intragenic mutation in PIK3CA coding sequence is determined in the body sample.

2. The method of claim 1 wherein the body sample is a first tissue that is suspected of being neoplastic, and the method further comprises the steps of:

   testing a second tissue that is not suspected of being neoplastic for the presence of the non-synonymous mutation, wherein the first and second tissue are isolated from the human;

   identifying the non-synonymous, intragenic mutation as somatic if said mutation is absent in the second tissue.

3. The method of claim 1 wherein the non-synonymous, intragenic mutation is in exon 9 (SEQ ID NO: 4).
4. The method of claim 1 wherein the non-synonymous, intragenic mutation is in exon 20 (SEQ ID NO: 5).
5. The method of claim 1 wherein the non-synonymous, intragenic mutation is in PIK3CA's helical domain (nt 1567-2124 of SEQ ID NO: 2).
6. The method of claim 1 wherein the non-synonymous, intragenic mutation is in PIK3CA's kinase domain (nt 2095-3096 of SEQ ID NO: 2).
7. The method of claim 1 wherein the non-synonymous, intragenic mutation is in PIK3CA's P85BD domain (nt 103-335 of SEQ ID NO: 2).
8. The method of claim 1 wherein the body sample is colorectal tissue.
9. The method of claim 1 wherein the body sample is brain tissue.
10. The method of claim 1 wherein the body sample is gastric tissue.
11. The method of claim 1 wherein the body sample is breast tissue.

12. The method of claim 1 wherein the body sample is lung tissue.
13. The method of claim 1 wherein the body sample is blood, serum, or plasma.
14. The method of claim 1 wherein the body sample is sputum.
15. The method of claim 1 wherein the body sample is saliva.
16. The method of claim 1 wherein the body sample is urine.
17. The method of claim 1 wherein the body sample is stool.
18. The method of claim 1 wherein the body sample is nipple aspirate.
19. The method of claim 1 wherein PIK3CA exons consisting of 9 and 20 are tested to determine a non-synonymous mutation.
20. The method of claim 1 wherein PIK3CA exons comprising 9 and 20 are tested to determine a non-synonymous mutation.
21. The method of claim 1 wherein the non-synonymous, intragenic mutation is a substitution mutation.
22. The method of claim 1 wherein the non-synonymous, intragenic mutation is G1624A.
23. The method of claim 1 wherein the non-synonymous, intragenic mutation is G1633A.
24. The method of claim 1 wherein the non-synonymous, intragenic mutation is C1636A.
25. The method of claim 1 wherein the non-synonymous, intragenic mutation is A3140G.
26. The method of claim 1 wherein the body sample is tested for mutations at nucleotide positions 1624, 1633, 1636, and 3140 of PIK3CA coding sequence.
27. The method of claim 1 wherein the body sample is tested for mutations G1624A, G1633A, C1636A, and A3140G.
28. The method of claim 21 wherein the body sample is further tested for mutations G113A, T1258C, G3129T, and C3139T.
29. The method of claim 27 wherein the body sample is further tested for mutation G2702T.
30. The method of claim 1 wherein the non-synonymous, intragenic mutation is a deletion mutation.
31. A method of inhibiting progression of a tumor in a human, comprising the steps of:

    administering to the human an antisense oligonucleotide or antisense construct to a tumor, wherein the antisense oligonucleotide or RNA transcribed from the antisense construct is complementary to mRNA transcribed from PIK3CA

(SEQ ID NO: 2), whereby amount of p110α protein expressed by the tumor is reduced.

32. The method of claim 31 wherein the antisense oligonucleotide or RNA transcribed from the antisense construct are complementary to a region of said mRNA which comprises an initial methionine codon of said mRNA.

33. A method of inhibiting progression of a tumor in a human, comprising the steps of:

administering to the human siRNA comprising 19 to 21 bp duplexes of a human PIK3CA mRNA with 2 nt 3' overhangs, wherein one strand of the duplex comprises a contiguous sequence selected from mRNA transcribed from PIK3CA (SEQ ID NO: 2), whereby amount of p110α protein expressed by the tumor is reduced.

34. The method of claim 33 wherein the contiguous sequence comprises an initial methionine codon of said mRNA.

35. A method of inhibiting progression of a tumor, comprising the steps of:

administering a molecule comprising an antibody binding region to a tumor, wherein the antibody binding region specifically binds to p110α (SEQ ID NO: 3).

36. The method of claim 35 wherein the antibody binding region specifically binds to the kinase domain (nt 2095-3096 of SEQ ID NO: 2) of PIK3CA.

37. The method of claim 35 wherein the antibody binding region specifically binds to the helical domain (nt 1567-2124 of SEQ ID NO: 2) of PIK3CA.

38. The method of claim 35 wherein the antibody binding region specifically binds to the P85BD domain (nt 103-335 of SEQ ID NO: 2) of PIK3CA.

39. A method of identifying candidate chemotherapeutic agents, comprising the steps of:

contacting a wild-type or activated mutant p110α (SEQ ID NO: 3) with a test compound;

measuring p110α activity;

identifying a test compound as a candidate chemotherapeutic agent if it inhibits p110α activity.

40. The method of claim 39 wherein a mutant form of the p110α is contacted with the test compound, said mutant form comprising a substitution mutation selected from the group consisting of E542K, E545K, Q546K, and H1047R.
41. The method of claim 39 wherein the test compound is identified as being a candidate chemotherapeutic agent for treating tumors with an activating mutation of p110α.
42. The method of claim 39 wherein the test compound is identified as being a candidate chemotherapeutic agent for treating tumors with a substitution mutation of PIK3CA.
43. The method of claim 39 wherein the test compound is identified as being a candidate chemotherapeutic agent for treating tumors with an activating mutation of PIK3CA in its kinase domain (nt 2095-3096 of SEQ ID NO: 2).
44. The method of claim 39 wherein the test compound is identified as being a candidate chemotherapeutic agent for treating tumors with an activating mutation of PIK3CA in its helical domain (nt 1567-2124 of SEQ ID NO: 2).
45. The method of claim 39 wherein the test compound is identified as being a candidate chemotherapeutic agent for treating tumors with an activating mutation of PIK3CA in its P85BD domain (nt 103-335 of SEQ ID NO: 2).
46. The method of claim 39 further comprising the steps of:

    contacting the test compound with one or more enzymes selected from the group consisting of: PIK3CB, PIK3CG, PIK3C2A, PIK3C2B, PIK3C2G, PIK3C3, A-TM, ATR, FRAP1, LAT1-3TM,SMG1, PRKDC, and TRRAP;

    identifying a test compound as a specific candidate chemotherapeutic agent if it inhibits one or more of said enzymes less than it inhibits p110α.
47. The method of claim 46 wherein a test compound which inhibits PIK3CB, PIK3CG, PIK3C2A, PIK3C2B, PIK3C2G, and PIK3C3 less than it inhibits p110α (PIK3CA) is identified as a highly specific candidate chemotherapeutic agent.
48. The method of claim 46 wherein a test compound which inhibits p110α more than it inhibits PIK3CB and PIK3CG is identified as highly specific.
49. The method of claim 39 wherein the step of contacting is performed in a cell-free system.
50. The method of claim 39 wherein the step of contacting is performed in whole cells.

51. A method for delivering an appropriate chemotherapeutic drug to a patient in need thereof, comprising:

determining a non-synonymous, intragenic mutation in a PIK3CA coding sequence (SEQ ID NO: 1) in a body sample of a patient;

administering a p110α inhibitor to the patient.

52. The method of claim 51 wherein the p110α inhibitor is LY294002.

53. The method of claim 51 wherein the p110α inhibitor is wortmannin.

54. The method of claim 51 wherein the p110α inhibitor is a molecule comprising an antibody binding region specific for p110α.

55. The method of claim 54 wherein the antibody binding region binds to the kinase domain (nt 2095-3096 of SEQ ID NO: 2).

56. The method of claim 54 wherein the antibody binding region binds to the helical domain (nt 1567-2124 of SEQ ID NO: 2).

57. The method of claim 54 wherein the antibody binding region binds to the P85BD domain (nt 103-335 of SEQ ID NO: 2).

58. A set of one or more primers for amplifying and/or sequencing PIK3CA, said primers selected from the group consisting of forward primers, reverse primers and sequencing primers, wherein the forward primers are selected from the group consisting of: SEQ ID NO: 6 to 165, the reverse primers are selected from the group consisting of: SEQ ID NO: 166 to 325, and the sequencing primers are selected from the group consisting of: SEQ ID NO: 326 to 485.

59. The set of claim 58 wherein the one or more primers comprise at least one forward and one reverse primer for amplifying a segment of PIK3CA.

60. The set of claim 58 wherein the one or more primers comprise at least one forward, one reverse, and one sequencing primer for amplifying and sequencing a segment of PIK3CA.

61. The set of claim 58 wherein the one or more primers comprise all of said forward, reverse, and sequencing primers.

62. The set of claim 58 which is in a single divided or undivided container.

63. The set of claim 59 which is in a single divided or undivided container.

64. The set of claim 60 which is in a single divided or undivided container.

65. The set of claim 61 which is in a single divided or undivided container.

MUTATIONS OF THE PIK3CA GENE IN HUMAN CANCERS

Abstract of the Invention

Phosphatidylinositol 3-kinases (PI3Ks) are known to be important regulators of signaling pathways. To determine whether PI3Ks are genetically altered in cancers, we analyzed the sequences of the PI3K gene family and discovered that one family member, PIK3CA, is frequently mutated in cancers of the colon and other organs. The majority of mutations clustered near two positions within the PI3K helical or kinase domains. PIK3CA represents one of the most highly mutated oncogenes yet identified in human cancers and is useful as a diagnostic and therapeutic target.

Fig. 1

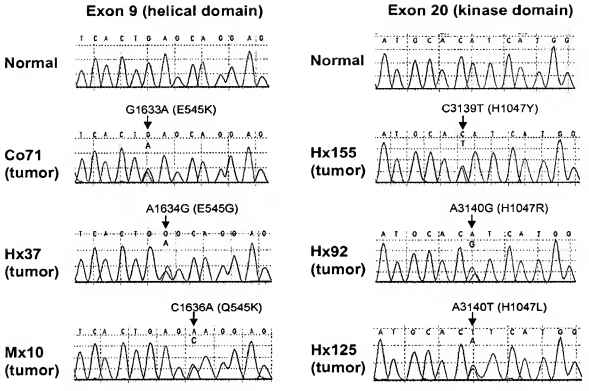

Exon 9 (helical domain)
Exon 20 (kinase domain)
Normal
Normal
G1633A (E545K)
C3139T (H1047Y)
Co71
(tumor)
Hx155
(tumor)
A1634G (E545G)
A3140G (H1047R)
Hx37
(tumor)
Hx92
(tumor)
C1636A (Q545K)
A3140T (H1047L)
Mx10
(tumor)
Hx125
(tumor)

Fig. 2

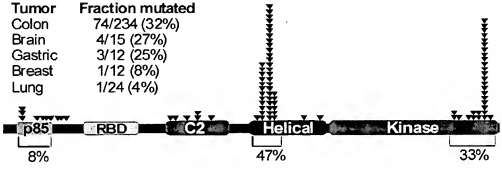
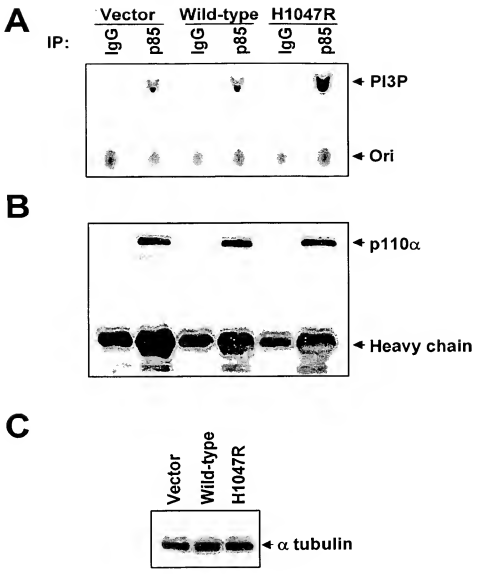

Tumor
Fraction mutated
Colon
74/234 (32%)
Brain
4/15 (27%)
Gastric
3/12 (25%)
Breast
1/12 (8%)
Lung
1/24 (4%)
p85
RBD
C2
Helical
Kinase
8%
47%
33%

Fig. 3


A
IP:
Vector
Wild-type
H1047R
IgG
p85
IgG
p85
IgG
p85
PI3P
Ori
B
p110α
Heavy chain
C
Vector
Wild-type
H1047R
α tubulin

Application Data Sheet

Application Information

Application number::	
Filing Date::	
Application Type::	Provisional
Subject Matter::	
Suggested classification::	
Suggested Group Art Unit::	
CD-ROM or CD-R?::	None
Number of CD disks::	
Number of copies of CDs::	
Sequence submission?::	PAPER
Computer Readable Form (CRF)?::	NO
Number of copies of CRF::	
Title::	Mutations of the PIK3CA Gene in Human Cancers
Attorney Docket Number::	001107.00428
Request for Early Publication?::	NO
Request for Non-Publication?::	NO
Suggested Drawing Figure::	
Total Drawing Sheets::	3
Small Entity?::	YES
Latin name::	
Variety denomination name::	
Petition included?::	NO
Petition Type::	
Licensed US Govt. Agency::	National Institutes of Health
Contract or Grant Numbers::	CA 43460, CA 62924
Secrecy Order in Parent Appl.?::	NO

Applicant Information

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Yardena
Middle Name::	
Family Name::	Samuels
Name Suffix::	
City of Residence::	Baltimore
State or Province of Residence::	Maryland
Country of Residence::	
Street of mailing address::	
City of mailing address::	Baltimore
State or Province of mailing address::	MD
Country of mailing address::	
Postal or Zip Code of mailing address::	

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Victor
Middle Name::	
Family Name::	Velculescu
Name Suffix::	
City of Residence::	Dayton
State or Province of Residence::	MD
Country of Residence::	
Street of mailing address::	14064 Big Branch Drive
City of mailing address::	Dayton

State or Province of mailing address::	MD
Country of mailing address::	
Postal or Zip Code of mailing address::	21036

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Kenneth
Middle Name::	
Family Name::	Kinzler
Name Suffix::	
City of Residence::	Bel Air
State or Province of Residence::	MD
Country of Residence::	
Street of mailing address::	1403 Halkirk Way
City of mailing address::	Bel Air
State or Province of mailing address::	MD
Country of mailing address::	
Postal or Zip Code of mailing address::	21015

Applicant Authority Type::	Inventor
Primary Citizenship Country::	US
Status::	Full Capacity
Given Name::	Bert
Middle Name::	
Family Name::	Vogelstein
Name Suffix::	
City of Residence::	Baltimore
State or Province of Residence::	MD

Country of Residence::

Street of mailing address:: 3700 Breton Way

City of mailing address:: Baltimore

State or Province of mailing address:: MD

Country of mailing address::

Postal or Zip Code of mailing address:: 21208

Correspondence Information

Correspondence Customer Number:: 22907

Representative Information

Representative Customer Number:: 22907

Domestic Priority Information

Application::	Continuity Type::	Parent Application::	Parent Filing Date::

Foreign Priority Information

Country::	Application number::	Filing Date::	Priority Claimed::

Assignee Information

Assignee name:: The Johns Hopkins University

Street of mailing address:: 3400 N. Charles St.

City of mailing address:: Baltimore

State or Province of mailing address:: MD

Country of mailing address::

Postal or Zip Code of mailing address:: 21218

SEQUENCE LISTING

<110> Velculescu, Victor
Kinzler, Kenneth
Vogelstein, Bert

<120> MUTATIONS OF THE PIK3CA GENE IN HUMAN CANCERS

<130> 001107.00428

<160> 487

<170> FastSEQ for Windows Version 4.0

<210> 1
<211> 3412
<212> DNA
<213> Homo sapiens

<400> 1
atgcctccaa gaccatcatc aggtgaactg tggggcatcc acttgatgcc cccaagaatc 60
ctagtggaat gtttactacc aaatggaatg atagtgactt tagaatgcct ccgtgaggct 120
acattagtaa ctataaagca tgaactattt aaagaagcaa gaaaatatccc tctccatcaa 180
cttcttcaag atgaatcttc ttacattttc gtaagtgtta cccaagaagc agaaaggaa 240
gaatttttg atgaaacaag acgactttgt gatcttcggc tttttcaacc atttttaaaa 300
gtaattgaac cagtaggcaa ccgtgaagaa aagatcctca atcgagaaat tggttttgct 360
atcggcatgc cagtgtgcga atttgatatg gttaaagatc ctgaagtaca ggacttccga 420
agaaatattc ttaatgtttg taaagaagct gtggatctta gggatcttaa ttcacctcat 480
agtagagcaa tgtatgtcta tccgccacat gtagaatctt caccagagct gccaaagcac 540
atatataata aattggatag aggccaaata atagtggtga tttgggtaat agttctctca 600
aataatgaca agcagaagta tactcctgaaa atcaaccatg actgtgtgcc agaacaagta 660
attgctgaag caatcaggaa aaaaactaga agtatgttgc tatcatctga acaattaaaa 720
ctctgtgttt tagaatatca gggcaagtac attttaaaag tgtgtggatg tgatgaatac 780
ttcctagaaa aatatcctct gagtcagtat aagtatatga gaagctgtat aatgcttggg 840
aggatgccca atttgaagat gatggctaaa gaaagccttt attctcaact gccaatggac 900
tgttttacaa tgccatctta ttccagacgc atttccacag ctacaccata tatgaatgga 960
gaaacatcta caaaatccct ttgggttata aatagagcac tcagaataaa aattctttgt 1020
gcaacctacg tgaatctaaa tattcgagac attgacaaga tttatgttcg aacaggtatc 1080
taccatggag gagaaccctt atgtgacaat gtgaacactc aaagagtacc ttgttccaat 1140
cccaggtgga atgaatggct gaattatgat atatacattc ctgatcttcc tcgtgctgct 1200
cgacttttgcc tttccatttg ctctgttaaa ggccgaaagg gtgctaaaga ggaacactgt 1260
ccattggcat ggggaaatat aaacttgttt gattacacag acactctagt atctggaaaa 1320
atggctttga atctttggcc agtacctcat ggattagaag atttgctgaa ccctattggt 1380
gttactggat caaatccaaa taaagaaact ccatgcttag agttggagtt tgactggttc 1440
agcagtgtgg taaagttccc agatatgtca gtgattgaag agcatgccaa ttggtctgta 1500
tcccgagaag caggatttag ctattcccac gcaggactga gtaacagact agctagagac 1560
aatgaattaa gggaaaatga caaagaacag ctcaaagcaa tttctacacg agatcctctc 1620
tctgaaatca ctgagcagga gaaagatttt ctatggagtc acagacacta ttgtgtaact 1680
atcccgaaaa ttctaccaa attgctctg tctgttaaat ggaattctag agatgaagta 1740
gcccagatgt attgcttggt aaaagattgg cctccaatca aacctgaaca ggctatggaa 1800
cttctggact gtaattaccc agatcctatg gttcgaggtt ttgctgttcg gtgcttggaa 1860
aaatatttaa cagatgacaa actttctcag tatttaattc agctagtaca ggtcctaaaa 1920
tatgaacaat atttggataa cttgcttgtg agatttttac tgaagaaagc attgactaat 1980
caaaggattg ggcacttttt cttttggcat ttaaaatctg agatgcacaa taaaacagtt 2040
agccagaggt ttggcctgct tttggagtcc tattgtcgtg catgtgggat gtatttgaag 2100
cacctgaata ggcaagtcga ggcaatggaa aagctcatta acttaactga cattctcaaa 2160
caggagagga aggatgaaac acaaaaggta cagatgaagt ttttagttga gcaaatgagg 2220
cgaccagatt tcatggatgc cctacagggc ttgctgtctc ctctaaaccc tgctcatcaa 2280
ctaggaaacc tcaggcttaa agagtgtcga attatgtctt ctgcaaaaag gccactgtgg 2340
ttgaattggg agaacccaga catcatgtca gagttactgt ttcagaacaa tgagatcatc 2400

```
tttaaaaatg gggatgattt acggcaagat atgctaacac ttcaaattat tcgtattatg     2460
gaaaatatct ggcaaaatca aggtcttgat cttcgaatgt taccttatgg ttgtctgtca     2520
atcggtgact gtgtgggact tattgaggtg gtgcgaaatt ctcacactat tatgcaaatt     2580
cagtgcaaag gcggcttgaa aggtgcactg cagttcaaca gccacacact acatcagtgg     2640
ctcaaagaca agaacaaagg agaaatatat gatgcagcca ttgacctgtt tacacgttca     2700
tgtgctggat actgtgtagc taccttcatt ttgggaattg gagatcgtca caatagtaac     2760
atcatggtga aagacgatgg acaactgttt catatagatt ttggacactt tttggatcac     2820
aagaagaaaa aatttggtta taaacgagaa cgtgtgccat ttgttttgac acaggatttc     2880
ttaatagtga ttagtaaagg agcccaagaa tgcacaaaga caagagaatt tgagaggttt     2940
caggagatgt gttacaaggc ttatctagct attcgacagc atgccaatct cttcataaat     3000
ctttttctaa tgatgcttgg ctctggaatg ccagaactac aatcttttga tgacattgca     3060
tacattcgaa agaccctagc cttagataaa actgagcaag aggctttgga gtatttcatg     3120
aaacaaatga atgatgcaca tcatggtggc tggacaacaa aaatggattg gatcttccac     3180
acaattaaac agcatgcatt gaactgaaag atcaactgaga aaatgaaagc tcactctgga     3240
ttccacactg cactgttaat aactctcagc aggcaaagac cgattgcata ggaattgcac     3300
aatccatgaa cagcattaga tttacagcaa gaacagaaat aaaatactat ataatttaaa     3360
taatgtaaac gcaaacaggg tttgatagca cttaaactag ttcatttcaa aa              3412

<210> 2
<211> 3424
<212> RNA
<213> Homo sapiens

<400> 2
aggatcagaa caatgcctcc aagaccatca tcaggtgaac tgtggggcat ccacttgatg       60
cccccaagaa tcctagtgga atgtttacta ccaaatggaa tgatagtgac tttagaatgc      120
ctccgtgagg ctacattagt aactataaag catgaactat ttaaagaagc aagaaaatac      180
cctctccatc aacttcttca agatgaatct tcttacattt tcgtaagtgt tacccaagaa      240
gcagaaaggg aagaattttt tgatgaaaca agacgacttt gtgatcttcg gctttttcaa      300
ccatttttaa aagtaattga accagtaggc aaccgtgaag aaaagatcct caatcgagaa      360
attggttttg ctatcggcat gccagtgtgc gaatttgata tggttaaaga tcctgaagta      420
caggacttcc gaagaaatat tcttaatgtt tgtaaagaag ctgtggatct tagggatctt      480
aattcacctc atagtagagc aatgtatgtc tatcggcaac atgtagaatc ttcaccagag      540
ctgccaaagc acatatataa taaattggat agaggtcaaa tcaatagtggt gatttgggta      600
atagtttctc caaataatga caagcagaag tatactctga aaatcaacca tgactgtgtg      660
ccagaacaag taattgctga agcaatcagg aaaaaaacta gaagtatgtt gctatcatct      720
gaacaattaa aactctgtgt tttagaatat cagggcaagt acattttaaa agtgtgtgga      780
tgtgatgaat acttcctaga aaaatatcct ctgagtcagt ataagtatat aagaagctgt      840
ataatgcttg ggaggatgcc caatttgaag atgatggcta aagaaagcct ttattctcaa      900
ctgccaatgg actgttttac aatgccatct tattccagac gcatttccac agctacacca      960
tatatgaatg gagaaacatc tacaaaatcc ctttgggtta taaatagagc agctcagaata    1020
aaaattcttt gtgcaaccta cgtgaatcta aatattcgag acattgacaa gatttatgtt    1080
cgaacaggta tctaccatgg aggagaaccc ttatgtgaca atgtgaacac tcaaagagta    1140
ccttgttcca atcccaggtg gaatgaatgg ctgaattatg atatatacat tcctgatctt    1200
cctcgtgctg ctcgactttg cctttccatt tgctctgtta aaggccgaaa gggtgctcaa    1260
gaggaacact gtccattggc atggggaaat ataaacttgt ttgattacac agacactcta    1320
gtatctggaa aaatggcttt gaatctttgg ccagtacctc atggattaga agatttgctg    1380
aaccctattg gtgttactgg atcaaatcca aataaagaaa ctccatgctt agagttggag    1440
tttgactggt tcagcagtgt ggtaaagttc ccagatatgt cagtgattga agagcatgcc    1500
aattggtctg tatccccgaga agcaggattt agctattccc acgcaggact gagtaacaga    1560
ctagctagag acaatgaatt aagggaaaat gacaaagaac agctcaaagc tgattgtcaa    1620
cgagatcctc tctctgaaat cactgagcag gagaaagatt ttctatggag tcacagacac    1680
tatttgttaa atatcccgga aattctaccc aaattgctcc tgtctgttaa atggaatttc    1740
agagatgaag tagcccagat gtattgcttg gtaaaagatt ggcctccaat caaacctgaa    1800
caggctatgg aacttctgga ctgtaattac ccagatccta tggttcgagg ttttgctgtt    1860
cggtgcttgg aaaaatattt aacagatgac aaactttctc agtatttaat tcagctagta    1920
caggtcctaa aatatgaaca atatttggat aacttgcttg tgagattttt actgaagaaa    1980
gcattgacta atcaaaggat tgggcacttt ttcttttggc atttaaaatc tgagatgcac    2040
aataaaacag ttagccagag gtttggcctg cttttggagt cctattgtcg tgcatgtggg    2100
atgtatttga agcacctgaa taggcaagtc gaggcaatgg aaaagctcat taacttaact    2160
gacattctca aacaggagag gaaggatgaa acacaaaagg tacagatgaa gtttttagtt    2220
gagcaaatga ggcgaccaga tttcatggat gccctacagg gcttgctgtc tcctctaaac    2280
cctgctcatc aactaggaaa cctcaggctt aaagagtgtc gaattatgtc ttctgcaaaa    2340
```

```
aggccactgt ggttgaattg ggagaaccca gacatcatgt cagagttact gtttcagaac    2400
aatgagatca tctttaaaaa tggggatgat ttacggcaag atatgctaac acttcaaatt    2460
attcgtatta tggaaaatat ctggcaaaat caaggtcttg atcttcgaat gttaccttat    2520
ggttgtctgt caatcggtga ctgtgtggga cttattgagg tggtgcgaaa ttctcacact    2580
attatgcaaa ttcagtgcaa aggcggcttg aaaggtgcac tgcagttcaa cagccacaca    2640
ctacatcagt ggctcaaaga caagaacaaa ggagaaatat atgatgcagc cattgacctg    2700
tttacacgtt catgtgctgg atactgtgta gctaccttca ttttgggaat tggagatcgt    2760
cacaatagta acatcatggt gaaagacgat ggacaactgt ttcatataga ttttggacac    2820
ttttttggatc acaagaagaa aaaatttggt tataaacgag aacgtgtgcc atttgttttg    2880
acacaggatt tcttaatagt gattagtaaa ggagcccaag aatgcacaaa gacaagagaa    2940
tttgagaggt ttcaggagat gtgttacaag gcttatctag ctattcgaca gcatgccaat    3000
ctcttcataa atcttttctc aatgatgctt ggctctggaa tgccagaact acaatctttt    3060
gatgacattg catacattcg aaagacccta gccttagata aaactgagca agaggctttg    3120
gagtatttca tgaaacaaat gaatgatgca catcatggtg gctggacaac aaaaatggat    3180
tggatcttcc acacaattaa acagcatgca ttgaactgaa agataactga gaaaatgaaa    3240
gctcactctg gattccacac tgcactgtta ataactctca gcaggcaaag accgattgca    3300
taggaattgc acaatccatg aacagcatta gatttacagc aagaacagaa ataaaatact    3360
atataattta aataatgtaa acgcaaacag ggtttgatag cacttaaact agttcatttc    3420
aaaa                                                                3424
```

<210> 3
<211> 1068
<212> PRT
<213> Homo sapiens

<400> 3

```
Met Pro Pro Arg Pro Ser Ser Gly Glu Leu Trp Gly Ile His Leu Met
 1               5                  10                  15
Pro Pro Arg Ile Leu Val Glu Cys Leu Leu Pro Asn Gly Met Ile Val
            20                  25                  30
Thr Leu Glu Cys Leu Arg Glu Ala Thr Leu Val Thr Ile Lys His Glu
        35                  40                  45
Leu Phe Lys Glu Ala Arg Lys Tyr Pro Leu His Gln Leu Leu Gln Asp
    50                  55                  60
Glu Ser Ser Tyr Ile Phe Val Ser Val Thr Gln Glu Ala Glu Arg Glu
65                  70                  75                  80
Glu Phe Phe Asp Glu Thr Arg Arg Leu Cys Asp Leu Arg Leu Phe Gln
                85                  90                  95
Pro Phe Leu Lys Val Ile Glu Pro Val Gly Asn Arg Glu Glu Lys Ile
            100                 105                 110
Leu Asn Arg Glu Ile Gly Phe Ala Ile Gly Met Pro Val Cys Glu Phe
        115                 120                 125
Asp Met Val Lys Asp Pro Glu Val Gln Asp Phe Arg Arg Asn Ile Leu
    130                 135                 140
Asn Val Cys Lys Glu Ala Val Asp Leu Arg Asp Leu Asn Ser Pro His
145                 150                 155                 160
Ser Arg Ala Met Tyr Val Tyr Pro Pro His Val Glu Ser Ser Pro Glu
                165                 170                 175
Leu Pro Lys His Ile Tyr Asn Lys Leu Asp Arg Gly Gln Ile Ile Val
            180                 185                 190
Val Ile Trp Val Ile Val Ser Pro Asn Asn Asp Lys Gln Lys Tyr Thr
        195                 200                 205
Leu Lys Ile Asn His Asp Cys Val Pro Glu Gln Val Ile Ala Glu Ala
    210                 215                 220
Ile Arg Lys Lys Thr Arg Ser Met Leu Leu Ser Ser Glu Gln Leu Lys
225                 230                 235                 240
Leu Cys Val Leu Glu Tyr Gln Gly Lys Tyr Ile Leu Lys Val Cys Gly
                245                 250                 255
Cys Asp Glu Tyr Phe Leu Glu Lys Tyr Pro Leu Ser Gln Tyr Lys Tyr
            260                 265                 270
Ile Arg Ser Cys Ile Met Leu Gly Arg Met Pro Asn Leu Lys Met Met
        275                 280                 285
Ala Lys Glu Ser Leu Tyr Ser Gln Leu Pro Met Asp Cys Phe Thr Met
```

```
    290                 295                 300
Pro Ser Tyr Ser Arg Arg Ile Ser Thr Ala Thr Pro Tyr Met Asn Gly
305                 310                 315                 320
Glu Thr Ser Thr Lys Ser Leu Trp Val Ile Asn Arg Ala Leu Arg Ile
                325                 330                 335
Lys Ile Leu Cys Ala Thr Tyr Val Asn Leu Asn Ile Arg Asp Ile Asp
            340                 345                 350
Lys Ile Tyr Val Arg Thr Gly Ile Tyr His Gly Gly Glu Pro Leu Cys
        355                 360                 365
Asp Asn Val Asn Thr Gln Arg Val Pro Cys Ser Asn Pro Arg Trp Asn
    370                 375                 380
Glu Trp Leu Asn Tyr Asp Ile Tyr Ile Pro Asp Leu Pro Arg Ala Ala
385                 390                 395                 400
Arg Leu Cys Leu Ser Ile Cys Ser Val Lys Gly Arg Lys Gly Ala Lys
                405                 410                 415
Glu Glu His Cys Pro Leu Ala Trp Gly Asn Ile Asn Leu Phe Asp Tyr
            420                 425                 430
Thr Asp Thr Leu Val Ser Gly Lys Met Ala Leu Asn Leu Trp Pro Val
        435                 440                 445
Pro His Gly Leu Glu Asp Leu Leu Asn Pro Ile Gly Val Thr Gly Ser
    450                 455                 460
Asn Pro Asn Lys Glu Thr Pro Cys Leu Glu Leu Glu Phe Asp Trp Phe
465                 470                 475                 480
Ser Ser Val Val Lys Phe Pro Asp Met Ser Val Ile Glu Glu His Ala
                485                 490                 495
Asn Trp Ser Val Ser Arg Glu Ala Gly Phe Ser Tyr Ser His Ala Gly
            500                 505                 510
Leu Ser Asn Arg Leu Ala Arg Asp Asn Glu Leu Arg Glu Asn Asp Lys
        515                 520                 525
Glu Gln Leu Lys Ala Ile Ser Thr Arg Asp Pro Leu Ser Glu Ile Thr
    530                 535                 540
Glu Gln Glu Lys Asp Phe Leu Trp Ser His Arg His Tyr Cys Val Thr
545                 550                 555                 560
Ile Pro Glu Ile Leu Pro Lys Leu Leu Leu Ser Val Lys Trp Asn Ser
                565                 570                 575
Arg Asp Glu Val Ala Gln Met Tyr Cys Leu Val Lys Asp Trp Pro Pro
            580                 585                 590
Ile Lys Pro Glu Gln Ala Met Glu Leu Leu Asp Cys Asn Tyr Pro Asp
        595                 600                 605
Pro Met Val Arg Gly Phe Ala Val Arg Cys Leu Glu Lys Tyr Leu Thr
    610                 615                 620
Asp Asp Lys Leu Ser Gln Tyr Leu Ile Gln Leu Val Gln Val Leu Lys
625                 630                 635                 640
Tyr Glu Gln Tyr Leu Asp Asn Leu Leu Val Arg Phe Leu Leu Lys Lys
                645                 650                 655
Ala Leu Thr Asn Gln Arg Ile Gly His Phe Phe Phe Trp His Leu Lys
            660                 665                 670
Ser Glu Met His Asn Lys Thr Val Ser Gln Arg Phe Gly Leu Leu Leu
        675                 680                 685
Glu Ser Tyr Cys Arg Ala Cys Gly Met Tyr Leu Lys His Leu Asn Arg
    690                 695                 700
Gln Val Glu Ala Met Glu Lys Leu Ile Asn Leu Thr Asp Ile Leu Lys
705                 710                 715                 720
Gln Glu Arg Lys Asp Glu Thr Gln Lys Val Gln Met Lys Phe Leu Val
                725                 730                 735
Glu Gln Met Arg Arg Pro Asp Phe Met Asp Ala Leu Gln Gly Leu Leu
            740                 745                 750
Ser Pro Leu Asn Pro Ala His Gln Leu Gly Asn Leu Arg Leu Lys Glu
        755                 760                 765
Cys Arg Ile Met Ser Ser Ala Lys Arg Pro Leu Trp Leu Asn Trp Glu
    770                 775                 780
Asn Pro Asp Ile Met Ser Glu Leu Leu Phe Gln Asn Asn Glu Ile Ile
785                 790                 795                 800
```

```
Phe Lys Asn Gly Asp Asp Leu Arg Gln Asp Met Leu Thr Leu Gln Ile
                805                 810                 815
Ile Arg Ile Met Glu Asn Ile Trp Gln Asn Gln Gly Leu Asp Leu Arg
            820                 825                 830
Met Leu Pro Tyr Gly Cys Leu Ser Ile Gly Asp Cys Val Gly Leu Ile
        835                 840                 845
Glu Val Val Arg Asn Ser His Thr Ile Met Gln Ile Gln Cys Lys Gly
    850                 855                 860
Gly Leu Lys Gly Ala Leu Gln Phe Asn Ser His Thr Leu His Gln Trp
865                 870                 875                 880
Leu Lys Asp Lys Asn Lys Gly Glu Ile Tyr Asp Ala Ala Ile Asp Leu
                885                 890                 895
Phe Thr Arg Ser Cys Ala Gly Tyr Cys Val Ala Thr Phe Ile Leu Gly
            900                 905                 910
Ile Gly Asp Arg His Asn Ser Asn Ile Met Val Lys Asp Asp Gly Gln
        915                 920                 925
Leu Phe His Ile Asp Phe Gly His Phe Leu Asp His Lys Lys Lys Lys
    930                 935                 940
Phe Gly Tyr Lys Arg Glu Arg Val Pro Phe Val Leu Thr Gln Asp Phe
945                 950                 955                 960
Leu Ile Val Ile Ser Lys Gly Ala Gln Glu Cys Thr Lys Thr Arg Glu
                965                 970                 975
Phe Glu Arg Phe Gln Glu Met Cys Tyr Lys Ala Tyr Leu Ala Ile Arg
            980                 985                 990
Gln His Ala Asn Leu Phe Ile Asn Leu Phe Ser Met Met Leu Gly Ser
        995                1000                1005
Gly Met Pro Glu Leu Gln Ser Phe Asp Asp Ile Ala Tyr Ile Arg Lys
    1010                1015                1020
Thr Leu Ala Leu Asp Lys Thr Glu Gln Glu Ala Leu Glu Tyr Phe Met
1025                1030                1035                1040
Lys Gln Met Asn Asp Ala His His Gly Gly Trp Thr Thr Lys Met Asp
                1045                1050                1055
Trp Ile Phe His Thr Ile Lys Gln His Ala Leu Asn
            1060                1065
```

<210> 4
<211> 125
<212> DNA
<213> Homo sapiens

<400> 4

```
agtaacagac tagctagaga caatgaatta agggaaaatg acaaagaaca gctcaaagca      60
atttctacac gagatcctct ctctgaaatc actgagcagg agaaagattt tctatggagt     120
cacag                                                                 125
```

<210> 5
<211> 1186
<212> DNA
<213> Homo sapiens

<400> 5

```
gtttcaggag atgtgttaca aggcttatct agctattcga cagcatgcca atctcttcat      60
aaatcttttc tcaatgatgc ttggctctgg aatgccagaa ctacaatctt ttgatgacat     120
tgcatacatt cgaaagaccc tagccttaga taaaactgag caaggaggctt tggagtattt     180
catgaaacaa atgaatgatg cacatcatgg tggctggaca acaaaaatgg attggatctt     240
ccacacaatt aaacagcatg cattgaactg aaaagataac tgaggaaatg aaagctcact     300
ctggattcca cactgcactg ttaataactc tcagcaggca aagaccgatt gcataggaat     360
tgcacaatcc atgaacagca ttagaattta cagcaagaac agaaataaaa tactatataa     420
tttaaataat gtaaacgcaa acagggtttg atagcactta aactagttca tttcaaaatt     480
aagctttaga ataatgcgca atttcatgtt atgccttaag tccaaaaagg taaacttga      540
agattgtttg tatctttttt taaaaaacaa aacaaaacaa aaatccccaa aatatataga     600
aatgatggag aaggaaaaag tgatggtttt ttttgtcttg caaatgttct atgttttgaa     660
atgtggacac aacaaaggct gttattgcat taggtgtaag taaactggag tttatgttaa     720
```

attacattga ttggaaaaga atgaaaattt cttatttttc cattgctgtt caatttatag 780
tttgaagtgg gtttttgact gcttgtttaa tgaagaaaaa tgcttggggt ggaagggact 840
cttgagattt caccagagac tttttctttt taataaatca aacctttga tgatttgagg 900
ttttatctgc agttttggaa gcagtcacaa atgagacctg ttataaggtg gtatttttt 960
ttttcttctg gacagtattt aaaggatctt attcttattt cccagggaaa ttctgggctc 1020
ccacaaagta aaaaaaaaa aaaatcatag aaaaagaatg agcaggaata gttcttattc 1080
cagaattgta cagtattcac cttaagttga ttttttttct ccttctgcaa ttgaactgaa 1140
tacatttttc atgcatgttt tccagaaaat agaagtatta atgtta 1186

<210> 6
<211> 20
<212> DNA
<213> Homo sapiens

<400> 6
ttccagcctg ggtaacaaag 20

<210> 7
<211> 20
<212> DNA
<213> Homo sapiens

<400> 7
cctgacctca ggtgttctgc 20

<210> 8
<211> 21
<212> DNA
<213> Homo sapiens

<400> 8
tgcacattct gcacgtgtat c 21

<210> 9
<211> 24
<212> DNA
<213> Homo sapiens

<400> 9
tcccagtttg tatgctattg agag 24

<210> 10
<211> 21
<212> DNA
<213> Homo sapiens

<400> 10
tggaaattca aaagtgtgtg g 21

<210> 11
<211> 23
<212> DNA
<213> Homo sapiens

<400> 11
cactaatgaa cccctcaaga ctg 23

<210> 12
<211> 20
<212> DNA
<213> Homo sapiens

<400> 12

tccttggcaa agtgacaatc 20

<210> 13
<211> 23
<212> DNA
<213> Homo sapiens

<400> 13
ctctcacata caacaccatc tcc 23

<210> 14
<211> 23
<212> DNA
<213> Homo sapiens

<400> 14
atgtatctca ttgaaaaccc aac 23

<210> 15
<211> 20
<212> DNA
<213> Homo sapiens

<400> 15
tcccaaagtg ctgggattac 20

<210> 16
<211> 26
<212> DNA
<213> Homo sapiens

<400> 16
cctatgacat aaatgccagt acaaac 26

<210> 17
<211> 24
<212> DNA
<213> Homo sapiens

<400> 17
tcttttgttc agtcagcatc tctc 24

<210> 18
<211> 24
<212> DNA
<213> Homo sapiens

<400> 18
ttgagaattc agatgagaaa ccag 24

<210> 19
<211> 20
<212> DNA
<213> Homo sapiens

<400> 19
gaaggccact ctcaaacctg 20

<210> 20
<211> 20
<212> DNA
<213> Homo sapiens

<400> 20
tcaaggcttg catttcattg 20

<210> 21
<211> 20
<212> DNA
<213> Homo sapiens

<400> 21
ttccacactc caaagaatgc 20

<210> 22
<211> 21
<212> DNA
<213> Homo sapiens

<400> 22
aattgcaatc ctcttggtag c 21

<210> 23
<211> 19
<212> DNA
<213> Homo sapiens

<400> 23
gccaagacca agcaactcc 19

<210> 24
<211> 20
<212> DNA
<213> Homo sapiens

<400> 24
ataaacgacc gctggcctac 20

<210> 25
<211> 20
<212> DNA
<213> Homo sapiens

<400> 25
gtacatccgg ggacacaatg 20

<210> 26
<211> 20
<212> DNA
<213> Homo sapiens

<400> 26
accgggttct tccagctaag 20

<210> 27
<211> 20
<212> DNA
<213> Homo sapiens

<400> 27
caatgcgtgc gttaaatctg 20

<210> 28
<211> 18
<212> DNA
<213> Homo sapiens

<400> 28
cccaatgcca cggactac 18

<210> 29
<211> 20
<212> DNA
<213> Homo sapiens

<400> 29
atccagctgg ctctgatagg 20

<210> 30
<211> 20
<212> DNA
<213> Homo sapiens

<400> 30
ctggtgctga aactcgactg 20

<210> 31
<211> 20
<212> DNA
<213> Homo sapiens

<400> 31
gtctcgttct ctccctcacg 20

<210> 32
<211> 18
<212> DNA
<213> Homo sapiens

<400> 32
cacaacctcg cccagttc 18

<210> 33
<211> 21
<212> DNA
<213> Homo sapiens

<400> 33
agcatcaccc tcagagcata c 21

<210> 34
<211> 22
<212> DNA
<213> Homo sapiens

<400> 34
tgccatacct cttaggcact tc 22

<210> 35
<211> 20
<212> DNA
<213> Homo sapiens

<400> 35
cgacagagca agattccatc 20

<210> 36
<211> 20
<212> DNA

<213> Homo sapiens

<400> 36
agattgccat ctgaggaagg 20

<210> 37
<211> 20
<212> DNA
<213> Homo sapiens

<400> 37
gcatggagag gaagtgaacc 20

<210> 38
<211> 22
<212> DNA
<213> Homo sapiens

<400> 38
tggccagaga gtttgattta tg 22

<210> 39
<211> 20
<212> DNA
<213> Homo sapiens

<400> 39
ccctcaatct cttgggaaag 20

<210> 40
<211> 21
<212> DNA
<213> Homo sapiens

<400> 40
tggtttcttc tcatggacag g 21

<210> 41
<211> 20
<212> DNA
<213> Homo sapiens

<400> 41
gggtgtccac acttctcagg 20

<210> 42
<211> 20
<212> DNA
<213> Homo sapiens

<400> 42
ccggaagaaa caatgagcag 20

<210> 43
<211> 20
<212> DNA
<213> Homo sapiens

<400> 43
ggtgtgagct gagtgagcag 20

<210> 44
<211> 20

<212> DNA
<213> Homo sapiens

<400> 44
gtgggaatga ccttcctttc 20

<210> 45
<211> 21
<212> DNA
<213> Homo sapiens

<400> 45
ggatgaacag gcagatgtga g 21

<210> 46
<211> 20
<212> DNA
<213> Homo sapiens

<400> 46
agccccttct atccagtgtg 20

<210> 47
<211> 20
<212> DNA
<213> Homo sapiens

<400> 47
tgcccacagc atctgtctac 20

<210> 48
<211> 20
<212> DNA
<213> Homo sapiens

<400> 48
attgtgtgcc agtcatttgc 20

<210> 49
<211> 21
<212> DNA
<213> Homo sapiens

<400> 49
ttccacatta agcatgagca c 21

<210> 50
<211> 27
<212> DNA
<213> Homo sapiens

<400> 50
gacagtcatt cttttcatag gtcatag 27

<210> 51
<211> 23
<212> DNA
<213> Homo sapiens

<400> 51
ccacatagta agccttcaat gac 23

<210> 52

<211> 23
<212> DNA
<213> Homo sapiens

<400> 52
tgaaaaatgt tcctttattc ttg 23

<210> 53
<211> 21
<212> DNA
<213> Homo sapiens

<400> 53
tctgagaaca ttccctgatc c 21

<210> 54
<211> 23
<212> DNA
<213> Homo sapiens

<400> 54
tcagctctct aatcctgaac tgc 23

<210> 55
<211> 23
<212> DNA
<213> Homo sapiens

<400> 55
agcagagaag aaacatatac cat 23

<210> 56
<211> 20
<212> DNA
<213> Homo sapiens

<400> 56
cattttggga aaggaggttc 20

<210> 57
<211> 20
<212> DNA
<213> Homo sapiens

<400> 57
attacaggcg tgagccactg 20

<210> 58
<211> 20
<212> DNA
<213> Homo sapiens

<400> 58
tttggcactg tcttcagagg 20

<210> 59
<211> 20
<212> DNA
<213> Homo sapiens

<400> 59
agagggaaca ccctttcctg 20

<210> 60
<211> 20
<212> DNA
<213> Homo sapiens

<400> 60
tatagcgttg tgcccatgac 20

<210> 61
<211> 26
<212> DNA
<213> Homo sapiens

<400> 61
tcctgcctct ttgctatttt tcaatg 26

<210> 62
<211> 22
<212> DNA
<213> Homo sapiens

<400> 62
ttgcctcaga gagatcatca ag 22

<210> 63
<211> 20
<212> DNA
<213> Homo sapiens

<400> 63
taggggcgct aatcgtactg 20

<210> 64
<211> 21
<212> DNA
<213> Homo sapiens

<400> 64
tctgatatgc atcagccact g 21

<210> 65
<211> 20
<212> DNA
<213> Homo sapiens

<400> 65
tgatttcaag ggaagcagag 20

<210> 66
<211> 20
<212> DNA
<213> Homo sapiens

<400> 66
tgtagaaagc aaggctgctc 20

<210> 67
<211> 20
<212> DNA
<213> Homo sapiens

<400> 67
accccaaagt catccaagtg 20

<210> 68
<211> 20
<212> DNA
<213> Homo sapiens

<400> 68
aaaggctcca gttgatggac 20

<210> 69
<211> 24
<212> DNA
<213> Homo sapiens

<400> 69
ccattaaaac cactctaagt cagg 24

<210> 70
<211> 21
<212> DNA
<213> Homo sapiens

<400> 70
aagcctcctc cagaaaagaa g 21

<210> 71
<211> 20
<212> DNA
<213> Homo sapiens

<400> 71
ccctcctgtc cactgagatg 20

<210> 72
<211> 20
<212> DNA
<213> Homo sapiens

<400> 72
tctcaagctg cctcacaatg 20

<210> 73
<211> 20
<212> DNA
<213> Homo sapiens

<400> 73
aaagacattg ccatgcaaac 20

<210> 74
<211> 20
<212> DNA
<213> Homo sapiens

<400> 74
ttgttgggct ccaaataaac 20

<210> 75
<211> 20
<212> DNA
<213> Homo sapiens

<400> 75

ccctggagtg cttacatgag 20

<210> 76
<211> 27
<212> DNA
<213> Homo sapiens

<400> 76
gactttataa acactcgaca ttagagc 27

<210> 77
<211> 20
<212> DNA
<213> Homo sapiens

<400> 77
atgatgacct ctggcaggac 20

<210> 78
<211> 20
<212> DNA
<213> Homo sapiens

<400> 78
gaatcaaccg tcagcgtgtc 20

<210> 79
<211> 21
<212> DNA
<213> Homo sapiens

<400> 79
ctggcaccgg ggaaaacaga g 21

<210> 80
<211> 22
<212> DNA
<213> Homo sapiens

<400> 80
tggacatcga ctacaagtct gg 22

<210> 81
<211> 20
<212> DNA
<213> Homo sapiens

<400> 81
tccttggggt tttgaagaag 20

<210> 82
<211> 20
<212> DNA
<213> Homo sapiens

<400> 82
aaggccttcc agactcttgc 20

<210> 83
<211> 21
<212> DNA
<213> Homo sapiens

<400> 83
cctctttgtt tttccctacc g 21

<210> 84
<211> 20
<212> DNA
<213> Homo sapiens

<400> 84
cttccacagt gggggtacag 20

<210> 85
<211> 23
<212> DNA
<213> Homo sapiens

<400> 85
gacacaacgg caacattatg ctg 23

<210> 86
<211> 23
<212> DNA
<213> Homo sapiens

<400> 86
cattccaaag catctggttt tac 23

<210> 87
<211> 22
<212> DNA
<213> Homo sapiens

<400> 87
ttgtgaggaa cgtgtgatta gg 22

<210> 88
<211> 19
<212> DNA
<213> Homo sapiens

<400> 88
ctgggcaaca gagcaagac 19

<210> 89
<211> 20
<212> DNA
<213> Homo sapiens

<400> 89
tcccttctcc tttggctatg 20

<210> 90
<211> 20
<212> DNA
<213> Homo sapiens

<400> 90
atagcaccac tgccttccag 20

<210> 91
<211> 19
<212> DNA
<213> Homo sapiens

<400> 91
tgcagaagtg gaggtggag 19

<210> 92
<211> 20
<212> DNA
<213> Homo sapiens

<400> 92
aacccaagct gcttcctttc 20

<210> 93
<211> 20
<212> DNA
<213> Homo sapiens

<400> 93
agtcctgccc tgattccttc 20

<210> 94
<211> 20
<212> DNA
<213> Homo sapiens

<400> 94
cccacccact tattcctgag 20

<210> 95
<211> 22
<212> DNA
<213> Homo sapiens

<400> 95
tttccccttt agggtaggta gg 22

<210> 96
<211> 21
<212> DNA
<213> Homo sapiens

<400> 96
cggacataga ggaaggattg c 21

<210> 97
<211> 20
<212> DNA
<213> Homo sapiens

<400> 97
tggccaaact tttcaaatcc 20

<210> 98
<211> 20
<212> DNA
<213> Homo sapiens

<400> 98
tgggagagct cagggaatac 20

<210> 99
<211> 20
<212> DNA

<213> Homo sapiens

<400> 99
tcccaaagtg ctgggattac 20

<210> 100
<211> 20
<212> DNA
<213> Homo sapiens

<400> 100
ttggctgcca tgactaacac 20

<210> 101
<211> 20
<212> DNA
<213> Homo sapiens

<400> 101
gctctcagtg tgcctcatgg 20

<210> 102
<211> 18
<212> DNA
<213> Homo sapiens

<400> 102
aagaaacacc ccggttcc 18

<210> 103
<211> 27
<212> DNA
<213> Homo sapiens

<400> 103
aaatttagtt gagtaatgag agaatgc 27

<210> 104
<211> 20
<212> DNA
<213> Homo sapiens

<400> 104
gtaaaattgg ccctgctttg 20

<210> 105
<211> 20
<212> DNA
<213> Homo sapiens

<400> 105
cataaccaca tgcagcaacc 20

<210> 106
<211> 20
<212> DNA
<213> Homo sapiens

<400> 106
aattggcctt ggagacagac 20

<210> 107
<211> 21

<212> DNA
<213> Homo sapiens

<400> 107
ttcatgtgag caggtatgct g 21

<210> 108
<211> 20
<212> DNA
<213> Homo sapiens

<400> 108
ttgtgtacga ccctctggtg 20

<210> 109
<211> 20
<212> DNA
<213> Homo sapiens

<400> 109
tttgtacagt ggaggcaacg 20

<210> 110
<211> 23
<212> DNA
<213> Homo sapiens

<400> 110
cagctggtta tgtgtgttta tgg 23

<210> 111
<211> 20
<212> DNA
<213> Homo sapiens

<400> 111
tgtcctcatg gttgcttttc 20

<210> 112
<211> 20
<212> DNA
<213> Homo sapiens

<400> 112
cagggacatg ctatccaaag 20

<210> 113
<211> 21
<212> DNA
<213> Homo sapiens

<400> 113
tggtggaact tgtgtttttc c 21

<210> 114
<211> 20
<212> DNA
<213> Homo sapiens

<400> 114
tcatacggtt ttggcagctc 20

<210> 115

<211> 20
<212> DNA
<213> Homo sapiens

<400> 115
acagagggag aagggctcag 20

<210> 116
<211> 20
<212> DNA
<213> Homo sapiens

<400> 116
tgggacaatt ttcgcagaag 20

<210> 117
<211> 20
<212> DNA
<213> Homo sapiens

<400> 117
atgaagcatg ctgcctgatg 20

<210> 118
<211> 19
<212> DNA
<213> Homo sapiens

<400> 118
gggggccttt agaaggaag 19

<210> 119
<211> 21
<212> DNA
<213> Homo sapiens

<400> 119
tggagttcct gagaaatgag c 21

<210> 120
<211> 20
<212> DNA
<213> Homo sapiens

<400> 120
agagggaaca ccctttcctg 20

<210> 121
<211> 22
<212> DNA
<213> Homo sapiens

<400> 121
catgatgttg gagcttacat gc 22

<210> 122
<211> 20
<212> DNA
<213> Homo sapiens

<400> 122
cgggattgga gacagacatc 20

<210> 123
<211> 20
<212> DNA
<213> Homo sapiens

<400> 123
catcatggta cacgcactcc 20

<210> 124
<211> 21
<212> DNA
<213> Homo sapiens

<400> 124
ctcaatcaga gcctgaacca c 21

<210> 125
<211> 21
<212> DNA
<213> Homo sapiens

<400> 125
cccggcctaa agttgtagtt c 21

<210> 126
<211> 20
<212> DNA
<213> Homo sapiens

<400> 126
tgggagactg tcaagaggtg 20

<210> 127
<211> 20
<212> DNA
<213> Homo sapiens

<400> 127
ttcctccaag gagctttgtc 20

<210> 128
<211> 21
<212> DNA
<213> Homo sapiens

<400> 128
ttccctgtcc agactgttag c 21

<210> 129
<211> 22
<212> DNA
<213> Homo sapiens

<400> 129
ccggttatgc acatcattta ag 22

<210> 130
<211> 21
<212> DNA
<213> Homo sapiens

<400> 130
gcagccagag cagaagtaaa c 21

<210> 131
<211> 21
<212> DNA
<213> Homo sapiens

<400> 131
tctaatgaaa gcccactctg c 21

<210> 132
<211> 22
<212> DNA
<213> Homo sapiens

<400> 132
aagtgtgcat gatgtttgtt cc 22

<210> 133
<211> 20
<212> DNA
<213> Homo sapiens

<400> 133
gatgaccaag aatgcaaacg 20

<210> 134
<211> 23
<212> DNA
<213> Homo sapiens

<400> 134
atcatcttta agaacgggga tgg 23

<210> 135
<211> 18
<212> DNA
<213> Homo sapiens

<400> 135
cctcagatgc tggtgccg 18

<210> 136
<211> 20
<212> DNA
<213> Homo sapiens

<400> 136
tcttcatgcc ttggctctgg 20

<210> 137
<211> 20
<212> DNA
<213> Homo sapiens

<400> 137
tccgagagag tgggcaggta 20

<210> 138
<211> 19
<212> DNA
<213> Homo sapiens

<400> 138

gggcaggttt gtgggtcat 19

<210> 139
<211> 18
<212> DNA
<213> Homo sapiens

<400> 139
ggaactgggg gctctggg 18

<210> 140
<211> 22
<212> DNA
<213> Homo sapiens

<400> 140
gttttctgctt tgggacaacc at 22

<210> 141
<211> 19
<212> DNA
<213> Homo sapiens

<400> 141
ctccacgacc atcatcagg 19

<210> 142
<211> 20
<212> DNA
<213> Homo sapiens

<400> 142
ccccctccat caacttcttc 20

<210> 143
<211> 26
<212> DNA
<213> Homo sapiens

<400> 143
tcatcaaaaa tttgttttaa cctagc 26

<210> 144
<211> 24
<212> DNA
<213> Homo sapiens

<400> 144
ttctgaacgt ttgtaaagaa gctg 24

<210> 145
<211> 21
<212> DNA
<213> Homo sapiens

<400> 145
gcagcccgct cagatataaa c 21

<210> 146
<211> 23
<212> DNA
<213> Homo sapiens

<400> 146
tctgaaaatc aaccatgact gtg 23

<210> 147
<211> 22
<212> DNA
<213> Homo sapiens

<400> 147
tcttgtgctt caacgtaaat cc 22

<210> 148
<211> 20
<212> DNA
<213> Homo sapiens

<400> 148
tctcaactgc caatggactg 20

<210> 149
<211> 20
<212> DNA
<213> Homo sapiens

<400> 149
tagtggatga aggcagcaac 20

<210> 150
<211> 20
<212> DNA
<213> Homo sapiens

<400> 150
tgccttttcc aatcaatctc 20

<210> 151
<211> 20
<212> DNA
<213> Homo sapiens

<400> 151
ggggaaaaag gaaagaatgg 20

<210> 152
<211> 20
<212> DNA
<213> Homo sapiens

<400> 152
tttgctgaac cctattggtg 20

<210> 153
<211> 22
<212> DNA
<213> Homo sapiens

<400> 153
gattggttct ttcctgtctc tg 22

<210> 154
<211> 20
<212> DNA
<213> Homo sapiens

<400> 154
accttttgaa cagcatgcaa 20

<210> 155
<211> 27
<212> DNA
<213> Homo sapiens

<400> 155
aaaacaccct taacattatt tccatag 27

<210> 156
<211> 28
<212> DNA
<213> Homo sapiens

<400> 156
tttattctag atccatacaa cttccttt 28

<210> 157
<211> 21
<212> DNA
<213> Homo sapiens

<400> 157
ctgaaactca tggtggtttt g 21

<210> 158
<211> 21
<212> DNA
<213> Homo sapiens

<400> 158
gagtgttgct gctctgtgtt g 21

<210> 159
<211> 25
<212> DNA
<213> Homo sapiens

<400> 159
ggattcctaa ataaaaattg aggtg 25

<210> 160
<211> 23
<212> DNA
<213> Homo sapiens

<400> 160
ttgctttcct gaagtttctt ttg 23

<210> 161
<211> 20
<212> DNA
<213> Homo sapiens

<400> 161
ggggaaaggc agtaaaggtc 20

<210> 162
<211> 23
<212> DNA

<213> Homo sapiens

<400> 162
tccttattcg ttgtcagtga ttg 23

<210> 163
<211> 20
<212> DNA
<213> Homo sapiens

<400> 163
catggtgaaa gacgatggac 20

<210> 164
<211> 21
<212> DNA
<213> Homo sapiens

<400> 164
tggggtaaag ggaatcaaaa g 21

<210> 165
<211> 20
<212> DNA
<213> Homo sapiens

<400> 165
ttgcatacat tcgaaagacc 20

<210> 166
<211> 20
<212> DNA
<213> Homo sapiens

<400> 166
cgtcagaaca agaccctgtg 20

<210> 167
<211> 22
<212> DNA
<213> Homo sapiens

<400> 167
cccggccact aagttatttt tc 22

<210> 168
<211> 20
<212> DNA
<213> Homo sapiens

<400> 168
ctgccattaa atgcgtcttg 20

<210> 169
<211> 20
<212> DNA
<213> Homo sapiens

<400> 169
ctttgggcct ttttcattcc 20

<210> 170
<211> 20

<212> DNA
<213> Homo sapiens

<400> 170
tgtctggctt atttcacacg 20

<210> 171
<211> 24
<212> DNA
<213> Homo sapiens

<400> 171
aactttgac agcctactat gtgc 24

<210> 172
<211> 23
<212> DNA
<213> Homo sapiens

<400> 172
gaccattcat gaaagaaaca agc 23

<210> 173
<211> 23
<212> DNA
<213> Homo sapiens

<400> 173
ccatgtaccg gtaacaaaag aag 23

<210> 174
<211> 23
<212> DNA
<213> Homo sapiens

<400> 174
tgagctttct aggatcgtac ctg 23

<210> 175
<211> 20
<212> DNA
<213> Homo sapiens

<400> 175
gcaggaaggt ccaacttgtc 20

<210> 176
<211> 20
<212> DNA
<213> Homo sapiens

<400> 176
atcttcaact gcgaacatgc 20

<210> 177
<211> 26
<212> DNA
<213> Homo sapiens

<400> 177
aagcatcaat gactacttta atcaac 26

<210> 178

<211> 20
<212> DNA
<213> Homo sapiens

<400> 178
tcccaaagtg ctgggattac 20

<210> 179
<211> 20
<212> DNA
<213> Homo sapiens

<400> 179
ttgttgcctt tgtcattttg 20

<210> 180
<211> 20
<212> DNA
<213> Homo sapiens

<400> 180
atgtgactgt gggcaggaac 20

<210> 181
<211> 20
<212> DNA
<213> Homo sapiens

<400> 181
gctggtgaga tgtcaaaacg 20

<210> 182
<211> 26
<212> DNA
<213> Homo sapiens

<400> 182
tcaacatatt acttcctcca gaactc 26

<210> 183
<211> 20
<212> DNA
<213> Homo sapiens

<400> 183
ttctcccatg tcagggaatc 20

<210> 184
<211> 20
<212> DNA
<213> Homo sapiens

<400> 184
gaccctcaaa ggctaacgtg 20

<210> 185
<211> 21
<212> DNA
<213> Homo sapiens

<400> 185
tccctggtca gcacagacta c 21

<210> 186
<211> 21
<212> DNA
<213> Homo sapiens

<400> 186
agctgtctca tttccaccat c 21

<210> 187
<211> 20
<212> DNA
<213> Homo sapiens

<400> 187
cgcgtcgttt atgtcaaatc 20

<210> 188
<211> 20
<212> DNA
<213> Homo sapiens

<400> 188
cgcgtcgttt atgtcaaatc 20

<210> 189
<211> 20
<212> DNA
<213> Homo sapiens

<400> 189
cataacacac aggggtgctg 20

<210> 190
<211> 18
<212> DNA
<213> Homo sapiens

<400> 190
gaactgggcg aggttgtg 18

<210> 191
<211> 20
<212> DNA
<213> Homo sapiens

<400> 191
tccctttctt acacgcaaac 20

<210> 192
<211> 21
<212> DNA
<213> Homo sapiens

<400> 192
cagttccgcc tgtacattca c 21

<210> 193
<211> 19
<212> DNA
<213> Homo sapiens

<400> 193
agcgctcctg ctttcagtc 19

<210> 194
<211> 20
<212> DNA
<213> Homo sapiens

<400> 194
gtcttggcgc agatcatcac 20

<210> 195
<211> 21
<212> DNA
<213> Homo sapiens

<400> 195
ttttgtcacc agttgaaatg c 21

<210> 196
<211> 20
<212> DNA
<213> Homo sapiens

<400> 196
gactgggaaa aagcatgagc 20

<210> 197
<211> 25
<212> DNA
<213> Homo sapiens

<400> 197
cggtgatcat aatattgtca ttgtg 25

<210> 198
<211> 20
<212> DNA
<213> Homo sapiens

<400> 198
ggaagtgtgg gcttgtcttc 20

<210> 199
<211> 20
<212> DNA
<213> Homo sapiens

<400> 199
tgcacagtcc atcctttgtc 20

<210> 200
<211> 21
<212> DNA
<213> Homo sapiens

<400> 200
aatgccagct ttcacaatgt c 21

<210> 201
<211> 20
<212> DNA
<213> Homo sapiens

<400> 201

ggccaagacc acatggtaag 20

<210> 202
<211> 24
<212> DNA
<213> Homo sapiens

<400> 202
tcctacatta agacagcatg gaac 24

<210> 203
<211> 21
<212> DNA
<213> Homo sapiens

<400> 203
tgcctcccttt ttaaggctat c 21

<210> 204
<211> 20
<212> DNA
<213> Homo sapiens

<400> 204
aggtccttct gccaacaaag 20

<210> 205
<211> 20
<212> DNA
<213> Homo sapiens

<400> 205
cgtcttctct cctccaatgc 20

<210> 206
<211> 20
<212> DNA
<213> Homo sapiens

<400> 206
ggtattcagt tggggctcag 20

<210> 207
<211> 20
<212> DNA
<213> Homo sapiens

<400> 207
tgtatccacg tggtcagctc 20

<210> 208
<211> 18
<212> DNA
<213> Homo sapiens

<400> 208
acaggacgct cggtcaac 18

<210> 209
<211> 25
<212> DNA
<213> Homo sapiens

<400> 209
ttgccatcag tacaaatgag tttag 25

<210> 210
<211> 24
<212> DNA
<213> Homo sapiens

<400> 210
ttcctgcttt ttaagagtga tctg 24

<210> 211
<211> 20
<212> DNA
<213> Homo sapiens

<400> 211
aggaaggaag ggatggaaac 20

<210> 212
<211> 18
<212> DNA
<213> Homo sapiens

<400> 212
agaaaccact catgaaaa 18

<210> 213
<211> 22
<212> DNA
<213> Homo sapiens

<400> 213
cgcattacta catgatccac tg 22

<210> 214
<211> 21
<212> DNA
<213> Homo sapiens

<400> 214
tgtcacagaa agcatgagac c 21

<210> 215
<211> 29
<212> DNA
<213> Homo sapiens

<400> 215
agaaataact gtcaatatcc cagtatcac 29

<210> 216
<211> 27
<212> DNA
<213> Homo sapiens

<400> 216
tcattaaaca tttagtaatg tgtgctc 27

<210> 217
<211> 19
<212> DNA
<213> Homo sapiens

<400> 217
aggcaacagg gcaagactc 19

<210> 218
<211> 21
<212> DNA
<213> Homo sapiens

<400> 218
cctgaaaggg agaataaaag g 21

<210> 219
<211> 21
<212> DNA
<213> Homo sapiens

<400> 219
cctgaaaggg agaataaaag g 21

<210> 220
<211> 20
<212> DNA
<213> Homo sapiens

<400> 220
tattgaccca gccagcagac 20

<210> 221
<211> 22
<212> DNA
<213> Homo sapiens

<400> 221
tatattgaga ctcaaatatc ga 22

<210> 222
<211> 21
<212> DNA
<213> Homo sapiens

<400> 222
tgatgcatat cagagcgtga g 21

<210> 223
<211> 21
<212> DNA
<213> Homo sapiens

<400> 223
ttcaatgacc atgacaaaac g 21

<210> 224
<211> 21
<212> DNA
<213> Homo sapiens

<400> 224
ttcaatgacc atgacaaaac g 21

<210> 225
<211> 21
<212> DNA

<213> Homo sapiens

<400> 225
tggttttcaa gcagacaatc c 21

<210> 226
<211> 21
<212> DNA
<213> Homo sapiens

<400> 226
tcctcctcaa tgaaagcaga g 21

<210> 227
<211> 20
<212> DNA
<213> Homo sapiens

<400> 227
caatgtgatc ccaactggtc 20

<210> 228
<211> 21
<212> DNA
<213> Homo sapiens

<400> 228
ttattgccaa ttggagtttg g 21

<210> 229
<211> 22
<212> DNA
<213> Homo sapiens

<400> 229
ttctgttggc ttatcatttt tg 22

<210> 230
<211> 23
<212> DNA
<213> Homo sapiens

<400> 230
cccagaaact aaataaaatg cag 23

<210> 231
<211> 25
<212> DNA
<213> Homo sapiens

<400> 231
aatcaaattt gttgcattaa aaatc 25

<210> 232
<211> 23
<212> DNA
<213> Homo sapiens

<400> 232
gttttctcat tcctttctct tcc 23

<210> 233
<211> 20

<212> DNA
<213> Homo sapiens

<400> 233
tttgggaaag ggaacacaag 20

<210> 234
<211> 22
<212> DNA
<213> Homo sapiens

<400> 234
gatttttcct tggaacatcc tc 22

<210> 235
<211> 20
<212> DNA
<213> Homo sapiens

<400> 235
cggggatcag atttgctatg 20

<210> 236
<211> 20
<212> DNA
<213> Homo sapiens

<400> 236
taggggtca tcctcaggtc 20

<210> 237
<211> 20
<212> DNA
<213> Homo sapiens

<400> 237
gtcttcccct gctcaatcac 20

<210> 238
<211> 22
<212> DNA
<213> Homo sapiens

<400> 238
gacacgttgt gggccagcca gt 22

<210> 239
<211> 24
<212> DNA
<213> Homo sapiens

<400> 239
ctgccggtta tcttcggaca cgtt 24

<210> 240
<211> 20
<212> DNA
<213> Homo sapiens

<400> 240
tgagtgaggg cagacagatg 20

<210> 241

<211> 20
<212> DNA
<213> Homo sapiens

<400> 241
tggcacctga accatgtaag 20

<210> 242
<211> 20
<212> DNA
<213> Homo sapiens

<400> 242
cgtacatgcc gaagtctgtc 20

<210> 243
<211> 21
<212> DNA
<213> Homo sapiens

<400> 243
gccctggttt taacccttaa c 21

<210> 244
<211> 20
<212> DNA
<213> Homo sapiens

<400> 244
ccagctccag cttctgactc 20

<210> 245
<211> 20
<212> DNA
<213> Homo sapiens

<400> 245
ttgtgttttc ttggagacag 20

<210> 246
<211> 20
<212> DNA
<213> Homo sapiens

<400> 246
caatgagcat gggagagatg 20

<210> 247
<211> 21
<212> DNA
<213> Homo sapiens

<400> 247
tggagtttct gggactacag g 21

<210> 248
<211> 23
<212> DNA
<213> Homo sapiens

<400> 248
ccttcttcaa agctgattct ctc 23

<210> 249
<211> 20
<212> DNA
<213> Homo sapiens

<400> 249
cgctctacag ccaatcacag 20

<210> 250
<211> 20
<212> DNA
<213> Homo sapiens

<400> 250
tggcatcaca atcaataggg 20

<210> 251
<211> 20
<212> DNA
<213> Homo sapiens

<400> 251
ctccaagggg gttagagtcc 20

<210> 252
<211> 21
<212> DNA
<213> Homo sapiens

<400> 252
caggaaacca ggtcagaagt g 21

<210> 253
<211> 22
<212> DNA
<213> Homo sapiens

<400> 253
tttttgcaga aaggggtctt ac 22

<210> 254
<211> 20
<212> DNA
<213> Homo sapiens

<400> 254
gcccacccca ctctagaaac 20

<210> 255
<211> 21
<212> DNA
<213> Homo sapiens

<400> 255
tggaaccttt tctgctcaaa g 21

<210> 256
<211> 18
<212> DNA
<213> Homo sapiens

<400> 256
agctgcatgg tgccaaag 18

<210> 257
<211> 20
<212> DNA
<213> Homo sapiens

<400> 257
ataacaatgg gcacatgcag 20

<210> 258
<211> 21
<212> DNA
<213> Homo sapiens

<400> 258
ggtcattctt ccatcagcaa g 21

<210> 259
<211> 21
<212> DNA
<213> Homo sapiens

<400> 259
cacacccaca ctcacacaaa g 21

<210> 260
<211> 20
<212> DNA
<213> Homo sapiens

<400> 260
ggcactgcag gctaataatg 20

<210> 261
<211> 22
<212> DNA
<213> Homo sapiens

<400> 261
gggacctcaa gtcttttcct tc 22

<210> 262
<211> 22
<212> DNA
<213> Homo sapiens

<400> 262
gggacctcaa gtcttttcct tc 22

<210> 263
<211> 20
<212> DNA
<213> Homo sapiens

<400> 263
ggaagggaag gaggacaaac 20

<210> 264
<211> 22
<212> DNA
<213> Homo sapiens

<400> 264

cgtctcaaac taccaagtct gg 22

<210> 265
<211> 20
<212> DNA
<213> Homo sapiens

<400> 265
cacccagtgc tgtttcaatg 20

<210> 266
<211> 20
<212> DNA
<213> Homo sapiens

<400> 266
cgccgcataa tgtgtaaaac 20

<210> 267
<211> 22
<212> DNA
<213> Homo sapiens

<400> 267
tgccatattt aactgccatt tc 22

<210> 268
<211> 22
<212> DNA
<213> Homo sapiens

<400> 268
tgccatattt aactgccatt tc 22

<210> 269
<211> 24
<212> DNA
<213> Homo sapiens

<400> 269
gcagtcactg agacagcttt tatc 24

<210> 270
<211> 20
<212> DNA
<213> Homo sapiens

<400> 270
taagcatagc ctcggagaac 20

<210> 271
<211> 24
<212> DNA
<213> Homo sapiens

<400> 271
ggaccattaa tagctacctt cctg 24

<210> 272
<211> 23
<212> DNA
<213> Homo sapiens

<400> 272
aggcaagaca acatatttga aag 23

<210> 273
<211> 23
<212> DNA
<213> Homo sapiens

<400> 273
aagggctatg tgtcattttg ttc 23

<210> 274
<211> 21
<212> DNA
<213> Homo sapiens

<400> 274
catcaagcaa gcaaacaaat g 21

<210> 275
<211> 19
<212> DNA
<213> Homo sapiens

<400> 275
aattccccca aaagcttcc 19

<210> 276
<211> 20
<212> DNA
<213> Homo sapiens

<400> 276
ttccctcctg gctaagaacc 20

<210> 277
<211> 20
<212> DNA
<213> Homo sapiens

<400> 277
aaaagcagag ggaatcatcg 20

<210> 278
<211> 20
<212> DNA
<213> Homo sapiens

<400> 278
tcccattcat gacctggaag 20

<210> 279
<211> 20
<212> DNA
<213> Homo sapiens

<400> 279
ggcccgcttt aagagatcag 20

<210> 280
<211> 18
<212> DNA
<213> Homo sapiens

<400> 280
catgcccaaa gtcgatcc 18

<210> 281
<211> 20
<212> DNA
<213> Homo sapiens

<400> 281
acacatccat ggtgttggtg 20

<210> 282
<211> 20
<212> DNA
<213> Homo sapiens

<400> 282
tgccacagcc acatagtctc 20

<210> 283
<211> 22
<212> DNA
<213> Homo sapiens

<400> 283
ttctatctgc agactcccac ag 22

<210> 284
<211> 21
<212> DNA
<213> Homo sapiens

<400> 284
ggaaaagaaa gcaggagaag c 21

<210> 285
<211> 21
<212> DNA
<213> Homo sapiens

<400> 285
aaatggagaa aagcctggtt c 21

<210> 286
<211> 19
<212> DNA
<213> Homo sapiens

<400> 286
aagcaatcct cccaccttg 19

<210> 287
<211> 22
<212> DNA
<213> Homo sapiens

<400> 287
ccttccttttt tcactcacac ac 22

<210> 288
<211> 25
<212> DNA

<213> Homo sapiens

<400> 288
tgatttaata atgaagatgg gttgg 25

<210> 289
<211> 20
<212> DNA
<213> Homo sapiens

<400> 289
actcagtacc ccaggcagag 20

<210> 290
<211> 20
<212> DNA
<213> Homo sapiens

<400> 290
tcaaactcct gggctcaaac 20

<210> 291
<211> 18
<212> DNA
<213> Homo sapiens

<400> 291
cagccacatc cccctatg 18

<210> 292
<211> 20
<212> DNA
<213> Homo sapiens

<400> 292
tgccttcttc cactcctttc 20

<210> 293
<211> 23
<212> DNA
<213> Homo sapiens

<400> 293
aagagtgaaa gcagagatgt tcc 23

<210> 294
<211> 21
<212> DNA
<213> Homo sapiens

<400> 294
actaagcctc aggagcagcc t 21

<210> 295
<211> 25
<212> DNA
<213> Homo sapiens

<400> 295
gatacttggg gaagagagac ctacc 25

<210> 296
<211> 19

<212> DNA
<213> Homo sapiens

<400> 296
gaggggagag gagggggag 19

<210> 297
<211> 20
<212> DNA
<213> Homo sapiens

<400> 297
cacaaacctg cccacattgc 20

<210> 298
<211> 18
<212> DNA
<213> Homo sapiens

<400> 298
cctgggcggc tcaactct 18

<210> 299
<211> 19
<212> DNA
<213> Homo sapiens

<400> 299
aggcgtttcc gtttatggc 19

<210> 300
<211> 23
<212> DNA
<213> Homo sapiens

<400> 300
ctgcttcttg agtaacactt acg 23

<210> 301
<211> 26
<212> DNA
<213> Homo sapiens

<400> 301
gattacgaag gtattggttt agacag 26

<210> 302
<211> 26
<212> DNA
<213> Homo sapiens

<400> 302
ggtgttaaaa atagttccat agttcg 26

<210> 303
<211> 20
<212> DNA
<213> Homo sapiens

<400> 303
tataagcagt ccctgccttc 20

<210> 304

<211> 20
<212> DNA
<213> Homo sapiens

<400> 304
tataagcagt ccctgccttc 20

<210> 305
<211> 20
<212> DNA
<213> Homo sapiens

<400> 305
ctgggcgaga gtgagattcc 20

<210> 306
<211> 19
<212> DNA
<213> Homo sapiens

<400> 306
atgaacccag gaggcagag 19

<210> 307
<211> 20
<212> DNA
<213> Homo sapiens

<400> 307
cggagatttg gatgttctcc 20

<210> 308
<211> 20
<212> DNA
<213> Homo sapiens

<400> 308
cggagatttg gatgttctcc 20

<210> 309
<211> 21
<212> DNA
<213> Homo sapiens

<400> 309
tttgtagaaa tggggtcttg c 21

<210> 310
<211> 21
<212> DNA
<213> Homo sapiens

<400> 310
aattcctgaa gctctcccaa g 21

<210> 311
<211> 20
<212> DNA
<213> Homo sapiens

<400> 311
tgctgaacca gtcaaactcc 20

<210> 312
<211> 23
<212> DNA
<213> Homo sapiens

<400> 312
ttgcaatatt ggtcctagag ttc 23

<210> 313
<211> 26
<212> DNA
<213> Homo sapiens

<400> 313
ccacaaatat caatttacaa ccattg 26

<210> 314
<211> 25
<212> DNA
<213> Homo sapiens

<400> 314
tggaaataat gttaagggtg ttttt 25

<210> 315
<211> 20
<212> DNA
<213> Homo sapiens

<400> 315
tctgcatggc cgatctaaag 20

<210> 316
<211> 26
<212> DNA
<213> Homo sapiens

<400> 316
aaagttgaga agctcatcac tggtac 26

<210> 317
<211> 21
<212> DNA
<213> Homo sapiens

<400> 317
tggttccaaa tcctaatctg c 21

<210> 318
<211> 23
<212> DNA
<213> Homo sapiens

<400> 318
ttgagggtag gagaatgaga gag 23

<210> 319
<211> 22
<212> DNA
<213> Homo sapiens

<400> 319
catgcatatt tcaaaggtca ag 22

<210> 320
<211> 26
<212> DNA
<213> Homo sapiens

<400> 320
tcaagtaaga ggaggatatg tcaaag 26

<210> 321
<211> 24
<212> DNA
<213> Homo sapiens

<400> 321
catcaaatat ttcaaaggtt gagc 24

<210> 322
<211> 20
<212> DNA
<213> Homo sapiens

<400> 322
gtcaaaacaa atggcacacg 20

<210> 323
<211> 20
<212> DNA
<213> Homo sapiens

<400> 323
ttacaggcat gaaccaccac 20

<210> 324
<211> 20
<212> DNA
<213> Homo sapiens

<400> 324
cctatgcaat cggtctttgc 20

<210> 325
<211> 21
<212> DNA
<213> Homo sapiens

<400> 325
ggggatttt gttttgtttt g 21

<210> 326
<211> 20
<212> DNA
<213> Homo sapiens

<400> 326
aaaggggaaa tgcgtaggac 20

<210> 327
<211> 20
<212> DNA
<213> Homo sapiens

<400> 327

tcccaaagtg ctgggattac 20

<210> 328
<211> 27
<212> DNA
<213> Homo sapiens

<400> 328
ccagaactta aagtgaaatt taaaaag 27

<210> 329
<211> 19
<212> DNA
<213> Homo sapiens

<400> 329
gcgaggcaaa acacaaagc 19

<210> 330
<211> 21
<212> DNA
<213> Homo sapiens

<400> 330
ttggaaatgg ctgtacctca g 21

<210> 331
<211> 19
<212> DNA
<213> Homo sapiens

<400> 331
tacttgagca gcccacagg 19

<210> 332
<211> 24
<212> DNA
<213> Homo sapiens

<400> 332
aaaggaatga aagtggtttt tgtc 24

<210> 333
<211> 23
<212> DNA
<213> Homo sapiens

<400> 333
tgcaatgtaa tagttttcca agg 23

<210> 334
<211> 22
<212> DNA
<213> Homo sapiens

<400> 334
cagcaaatga actaagccac ag 22

<210> 335
<211> 24
<212> DNA
<213> Homo sapiens

<400> 335
tgctatacta tttgcccaca aaac 24

<210> 336
<211> 24
<212> DNA
<213> Homo sapiens

<400> 336
gaatgcattt attcagagat gagg 24

<210> 337
<211> 21
<212> DNA
<213> Homo sapiens

<400> 337
tgctagacac ttgctggtca c 21

<210> 338
<211> 25
<212> DNA
<213> Homo sapiens

<400> 338
ttgatattaa agttgcacaa actgc 25

<210> 339
<211> 25
<212> DNA
<213> Homo sapiens

<400> 339
tcaattgtgt gacatatcac ctacc 25

<210> 340
<211> 24
<212> DNA
<213> Homo sapiens

<400> 340
tcactgtaga aatccaagta ccac 24

<210> 341
<211> 21
<212> DNA
<213> Homo sapiens

<400> 341
tctgcatcag tttgattctg c 21

<210> 342
<211> 22
<212> DNA
<213> Homo sapiens

<400> 342
aatgcacttt ttatttttatt ag 22

<210> 343
<211> 20
<212> DNA
<213> Homo sapiens

<400> 343
gaaaagtgcc ggttcttgag 20

<210> 344
<211> 20
<212> DNA
<213> Homo sapiens

<400> 344
gcctacacag tccgttttcc 20

<210> 345
<211> 19
<212> DNA
<213> Homo sapiens

<400> 345
agaggagcgt gtgttgcag 19

<210> 346
<211> 20
<212> DNA
<213> Homo sapiens

<400> 346
actctgacgg tggagctgag 20

<210> 347
<211> 24
<212> DNA
<213> Homo sapiens

<400> 347
gctcttggtg ctaagttaaa gagg 24

<210> 348
<211> 20
<212> DNA
<213> Homo sapiens

<400> 348
atccagctgg ctctgatagg 20

<210> 349
<211> 20
<212> DNA
<213> Homo sapiens

<400> 349
tgaacagcca gatcctctcc 20

<210> 350
<211> 20
<212> DNA
<213> Homo sapiens

<400> 350
gtcccacctt gttaggaagc 20

<210> 351
<211> 20
<212> DNA

<213> Homo sapiens

<400> 351
tggcattctg aaaacggttc 20

<210> 352
<211> 19
<212> DNA
<213> Homo sapiens

<400> 352
gcaaacagcc tggacaatc 19

<210> 353
<211> 22
<212> DNA
<213> Homo sapiens

<400> 353
cacatatttc tgtcccctgt tg 22

<210> 354
<211> 20
<212> DNA
<213> Homo sapiens

<400> 354
tgtggttctt tggagcacag 20

<210> 355
<211> 21
<212> DNA
<213> Homo sapiens

<400> 355
ccaaggtaca tttcggaaaa c 21

<210> 356
<211> 20
<212> DNA
<213> Homo sapiens

<400> 356
accagccctt tcctctttgtc 20

<210> 357
<211> 20
<212> DNA
<213> Homo sapiens

<400> 357
ttcttcctca tgccattgtg 20

<210> 358
<211> 19
<212> DNA
<213> Homo sapiens

<400> 358
gtggcatctg gctgtcatc 19

<210> 359
<211> 24

<212> DNA
<213> Homo sapiens

<400> 359
caattagttt tccttgagca ctcc 24

<210> 360
<211> 24
<212> DNA
<213> Homo sapiens

<400> 360
tcttctttat ccaggacatc tgtg 24

<210> 361
<211> 19
<212> DNA
<213> Homo sapiens

<400> 361
cctgggagag gtctggttc 19

<210> 362
<211> 20
<212> DNA
<213> Homo sapiens

<400> 362
ggcagcatct tggtctgaag 20

<210> 363
<211> 20
<212> DNA
<213> Homo sapiens

<400> 363
gagcacttgg gagacctgag 20

<210> 364
<211> 20
<212> DNA
<213> Homo sapiens

<400> 364
agggaagcat gagcacagtc 20

<210> 365
<211> 20
<212> DNA
<213> Homo sapiens

<400> 365
tgagttctgt ctggctgtgg 20

<210> 366
<211> 20
<212> DNA
<213> Homo sapiens

<400> 366
tgatgaggga tgagggaaac 20

<210> 367

<211> 20
<212> DNA
<213> Homo sapiens

<400> 367
agggttaggg agcctagctg 20

<210> 368
<211> 19
<212> DNA
<213> Homo sapiens

<400> 368
tccttggaac acccctgtc 19

<210> 369
<211> 25
<212> DNA
<213> Homo sapiens

<400> 369
cagtcatgat acctacactt ccatc 25

<210> 370
<211> 25
<212> DNA
<213> Homo sapiens

<400> 370
caactctgaa ataaaagcaa tctgg 25

<210> 371
<211> 25
<212> DNA
<213> Homo sapiens

<400> 371
ttctttggtt atgaaatgaa caatc 25

<210> 372
<211> 27
<212> DNA
<213> Homo sapiens

<400> 372
ttgaataaaa gtagatgttt cttgtcc 27

<210> 373
<211> 27
<212> DNA
<213> Homo sapiens

<400> 373
taccaagaat ataatacgtt gttatgg 27

<210> 374
<211> 20
<212> DNA
<213> Homo sapiens

<400> 374
cggcttctgg cacataaaac 20

<210> 375
<211> 23
<212> DNA
<213> Homo sapiens

<400> 375
ccattgagca ctccattcat tac 23

<210> 376
<211> 21
<212> DNA
<213> Homo sapiens

<400> 376
ccctgggaat ctgaaagaat g 21

<210> 377
<211> 20
<212> DNA
<213> Homo sapiens

<400> 377
tgggccgttg tctcatatac 20

<210> 378
<211> 20
<212> DNA
<213> Homo sapiens

<400> 378
cactctggct tttccctctg 20

<210> 379
<211> 20
<212> DNA
<213> Homo sapiens

<400> 379
aggtcatgaa tgggatcctg 20

<210> 380
<211> 19
<212> DNA
<213> Homo sapiens

<400> 380
catattgctt ggcgtccac 19

<210> 381
<211> 21
<212> DNA
<213> Homo sapiens

<400> 381
tcttggtgat ctttgccttt g 21

<210> 382
<211> 27
<212> DNA
<213> Homo sapiens

<400> 382
tcatcaagat tattcgatat ttgagtc 27

<210> 383
<211> 22
<212> DNA
<213> Homo sapiens

<400> 383
cgagaaagta aagtgcctgc tg 22

<210> 384
<211> 20
<212> DNA
<213> Homo sapiens

<400> 384
cgggattgga gacagacatc 20

<210> 385
<211> 19
<212> DNA
<213> Homo sapiens

<400> 385
gaggatgctg ccatttgtg 19

<210> 386
<211> 23
<212> DNA
<213> Homo sapiens

<400> 386
catgctaaca gagtgtcaag agc 23

<210> 387
<211> 20
<212> DNA
<213> Homo sapiens

<400> 387
cgaattcttt ttgccatttc 20

<210> 388
<211> 20
<212> DNA
<213> Homo sapiens

<400> 388
aaagtctgca aggggctatg 20

<210> 389
<211> 23
<212> DNA
<213> Homo sapiens

<400> 389
tcaggctaga aatgtatcca agg 23

<210> 390
<211> 20
<212> DNA
<213> Homo sapiens

<400> 390

aaaggaaagg ggtaatccag 20

<210> 391
<211> 27
<212> DNA
<213> Homo sapiens

<400> 391
tttacttttt atgattacct ctgatgc 27

<210> 392
<211> 27
<212> DNA
<213> Homo sapiens

<400> 392
aaagaaaatt caaatgaaaa taagtcg 27

<210> 393
<211> 22
<212> DNA
<213> Homo sapiens

<400> 393
catgcaaact tgggtctaga tg 22

<210> 394
<211> 20
<212> DNA
<213> Homo sapiens

<400> 394
ttggcttttt cccctcatac 20

<210> 395
<211> 20
<212> DNA
<213> Homo sapiens

<400> 395
taaagccttt cccagctcag 20

<210> 396
<211> 19
<212> DNA
<213> Homo sapiens

<400> 396
cctgctgctt ccacaggac 19

<210> 397
<211> 19
<212> DNA
<213> Homo sapiens

<400> 397
catggacgtc ctgtggaag 19

<210> 398
<211> 20
<212> DNA
<213> Homo sapiens

<400> 398
gtgtcccatt catcctcacc 20

<210> 399
<211> 19
<212> DNA
<213> Homo sapiens

<400> 399
aacagaggag gcgctgaag 19

<210> 400
<211> 18
<212> DNA
<213> Homo sapiens

<400> 400
gcctcaccct acccatcc 18

<210> 401
<211> 20
<212> DNA
<213> Homo sapiens

<400> 401
agattgctgg ggttcctttc 20

<210> 402
<211> 20
<212> DNA
<213> Homo sapiens

<400> 402
ccacctcact ccatctctgg 20

<210> 403
<211> 20
<212> DNA
<213> Homo sapiens

<400> 403
tggggtaagt tccctgagtg 20

<210> 404
<211> 20
<212> DNA
<213> Homo sapiens

<400> 404
tacagagcca gggagagtgc 20

<210> 405
<211> 20
<212> DNA
<213> Homo sapiens

<400> 405
tatcatccac atcggtcagc 20

<210> 406
<211> 25
<212> DNA
<213> Homo sapiens

<400> 406
tttgggacaa gtaattgtta ttagc 25

<210> 407
<211> 20
<212> DNA
<213> Homo sapiens

<400> 407
ttgaatgcag tggtgctctc 20

<210> 408
<211> 20
<212> DNA
<213> Homo sapiens

<400> 408
tctgcctgtg ttctgagctg 20

<210> 409
<211> 20
<212> DNA
<213> Homo sapiens

<400> 409
gaactcagct ctgcctggac 20

<210> 410
<211> 20
<212> DNA
<213> Homo sapiens

<400> 410
gcgagactcg gtctcaaaag 20

<210> 411
<211> 20
<212> DNA
<213> Homo sapiens

<400> 411
atcgtttgcc aactcctagc 20

<210> 412
<211> 20
<212> DNA
<213> Homo sapiens

<400> 412
aatcagtgca ggtgatgcag 20

<210> 413
<211> 20
<212> DNA
<213> Homo sapiens

<400> 413
acatggcctg tgtctgcttc 20

<210> 414
<211> 25
<212> DNA

<213> Homo sapiens

<400> 414
gactggaaga aaataaccaa gtttc 25

<210> 415
<211> 20
<212> DNA
<213> Homo sapiens

<400> 415
ggcaggcgtt aaaggaatag 20

<210> 416
<211> 19
<212> DNA
<213> Homo sapiens

<400> 416
aaaaacaggg cacccattg 19

<210> 417
<211> 20
<212> DNA
<213> Homo sapiens

<400> 417
ttaagcccac agggaacaag 20

<210> 418
<211> 20
<212> DNA
<213> Homo sapiens

<400> 418
tgtcagacct tggccttttc 20

<210> 419
<211> 23
<212> DNA
<213> Homo sapiens

<400> 419
tcttctgaaa aatggaggaa gtc 23

<210> 420
<211> 20
<212> DNA
<213> Homo sapiens

<400> 420
gctcttcctg gggaagtctc 20

<210> 421
<211> 20
<212> DNA
<213> Homo sapiens

<400> 421
cagtttttga ctgccactgc 20

<210> 422
<211> 21

<212> DNA
<213> Homo sapiens

<400> 422
tccatgctcg acactattct g 21

<210> 423
<211> 26
<212> DNA
<213> Homo sapiens

<400> 423
ttctacttta catacaaaag gcactc 26

<210> 424
<211> 20
<212> DNA
<213> Homo sapiens

<400> 424
agttgggctt agcctggatg 20

<210> 425
<211> 21
<212> DNA
<213> Homo sapiens

<400> 425
agtatcacgt ccatgttgga g 21

<210> 426
<211> 21
<212> DNA
<213> Homo sapiens

<400> 426
caatgtttgc tttgaaaaag g 21

<210> 427
<211> 20
<212> DNA
<213> Homo sapiens

<400> 427
tgagcaaaac ctgtggaatg 20

<210> 428
<211> 20
<212> DNA
<213> Homo sapiens

<400> 428
tttgctggtg ctgtctatgg 20

<210> 429
<211> 22
<212> DNA
<213> Homo sapiens

<400> 429
ggatgtgcaa aatgttcttc tg 22

<210> 430

<211> 21
<212> DNA
<213> Homo sapiens

<400> 430
gggagcaggt gttattgatt g 21

<210> 431
<211> 20
<212> DNA
<213> Homo sapiens

<400> 431
ggtgaggagt tttcccaagc 20

<210> 432
<211> 26
<212> DNA
<213> Homo sapiens

<400> 432
agcacagagt ttgttaatgt ttttag 26

<210> 433
<211> 23
<212> DNA
<213> Homo sapiens

<400> 433
gctgacttct attgggagca tac 23

<210> 434
<211> 21
<212> DNA
<213> Homo sapiens

<400> 434
cagaggtatg gtttgggtct c 21

<210> 435
<211> 21
<212> DNA
<213> Homo sapiens

<400> 435
tgggggtcta ggactatgga g 21

<210> 436
<211> 26
<212> DNA
<213> Homo sapiens

<400> 436
gctgtgtttt cttaatttcc tgtatg 26

<210> 437
<211> 19
<212> DNA
<213> Homo sapiens

<400> 437
cagcctcctg cagactttg 19

<210> 438
<211> 20
<212> DNA
<213> Homo sapiens

<400> 438
cattttggga aaggaggttc 20

<210> 439
<211> 20
<212> DNA
<213> Homo sapiens

<400> 439
cggtcagtat gacggtaggg 20

<210> 440
<211> 20
<212> DNA
<213> Homo sapiens

<400> 440
aggtcatgaa tgggatcctg 20

<210> 441
<211> 20
<212> DNA
<213> Homo sapiens

<400> 441
ggcgctaatc gtactgaaac 20

<210> 442
<211> 20
<212> DNA
<213> Homo sapiens

<400> 442
tatggtggcc atggagactg 20

<210> 443
<211> 19
<212> DNA
<213> Homo sapiens

<400> 443
aggagccctc ctttgattg 19

<210> 444
<211> 20
<212> DNA
<213> Homo sapiens

<400> 444
ggccagtggt atctgctgac 20

<210> 445
<211> 24
<212> DNA
<213> Homo sapiens

<400> 445
aagacaaaat cccaaataaa gcag 24

<210> 446
<211> 20
<212> DNA
<213> Homo sapiens

<400> 446
attggtttga gtgccctttg 20

<210> 447
<211> 22
<212> DNA
<213> Homo sapiens

<400> 447
aaaatgcttt gcactgactc tg 22

<210> 448
<211> 25
<212> DNA
<213> Homo sapiens

<400> 448
ttcatcttta ttgcccctat atctg 25

<210> 449
<211> 26
<212> DNA
<213> Homo sapiens

<400> 449
ttaaagatta taccaagtca gtggtc 26

<210> 450
<211> 20
<212> DNA
<213> Homo sapiens

<400> 450
catgtggttt cttgcctttg 20

<210> 451
<211> 24
<212> DNA
<213> Homo sapiens

<400> 451
aagcataggc tcagcatact acac 24

<210> 452
<211> 22
<212> DNA
<213> Homo sapiens

<400> 452
cccatcaact accatgtgac tg 22

<210> 453
<211> 22
<212> DNA
<213> Homo sapiens

<400> 453

ggtcctgttg tcagtttttc ag 22

<210> 454
<211> 20
<212> DNA
<213> Homo sapiens

<400> 454
ggtcctgggg tgctcctaga 20

<210> 455
<211> 22
<212> DNA
<213> Homo sapiens

<400> 455
tcctcaactg agccaagtag cc 22

<210> 456
<211> 22
<212> DNA
<213> Homo sapiens

<400> 456
tgtgtcctcc atgttctgtt gg 22

<210> 457
<211> 18
<212> DNA
<213> Homo sapiens

<400> 457
tggcccctct gcctagca 18

<210> 458
<211> 18
<212> DNA
<213> Homo sapiens

<400> 458
ccactgctgg gtcctggg 18

<210> 459
<211> 25
<212> DNA
<213> Homo sapiens

<400> 459
gaatagagag cttttcctga gatgc 25

<210> 460
<211> 24
<212> DNA
<213> Homo sapiens

<400> 460
gattcatctt gaagaagttg atgg 24

<210> 461
<211> 20
<212> DNA
<213> Homo sapiens

<400> 461
acttgatgcc cccaagaatc 20

<210> 462
<211> 21
<212> DNA
<213> Homo sapiens

<400> 462
ctcaagaagc agaaagggaa g 21

<210> 463
<211> 21
<212> DNA
<213> Homo sapiens

<400> 463
tctacagagt tccctgtttg c 21

<210> 464
<211> 21
<212> DNA
<213> Homo sapiens

<400> 464
gctgtggatc ttagggacct c 21

<210> 465
<211> 26
<212> DNA
<213> Homo sapiens

<400> 465
aaaaagcatt tctgatatgg ataaag 26

<210> 466
<211> 23
<212> DNA
<213> Homo sapiens

<400> 466
tcgaagtatg ttgctatcct ctg 23

<210> 467
<211> 25
<212> DNA
<213> Homo sapiens

<400> 467
aaaataataa gcatcagcat ttgac 25

<210> 468
<211> 21
<212> DNA
<213> Homo sapiens

<400> 468
ttattccaga cgcatttcca c 21

<210> 469
<211> 22
<212> DNA
<213> Homo sapiens

<400> 469
tttgagtcta tcgagtgtgt gc 22

<210> 470
<211> 21
<212> DNA
<213> Homo sapiens

<400> 470
ttcctgtttt tcgtttggtt g 21

<210> 471
<211> 21
<212> DNA
<213> Homo sapiens

<400> 471
tgaattttcc ttttggggaa g 21

<210> 472
<211> 25
<212> DNA
<213> Homo sapiens

<400> 472
tggatcaaat ccaaataaag taagg 25

<210> 473
<211> 25
<212> DNA
<213> Homo sapiens

<400> 473
ttgctttttc tgtaaatcat ctgtg 25

<210> 474
<211> 22
<212> DNA
<213> Homo sapiens

<400> 474
tatttcattt atttatgtgg ac 22

<210> 475
<211> 25
<212> DNA
<213> Homo sapiens

<400> 475
gaagttaagg cagtgtttta gatgg 25

<210> 476
<211> 25
<212> DNA
<213> Homo sapiens

<400> 476
accagtaata tccactttct ttctg 25

<210> 477
<211> 24
<212> DNA

<213> Homo sapiens

<400> 477
tttattggat ttcaaaaatg agtg 24

<210> 478
<211> 25
<212> DNA
<213> Homo sapiens

<400> 478
tctcatgtga gaaagagatt agcag 25

<210> 479
<211> 22
<212> DNA
<213> Homo sapiens

<400> 479
tggctttcag tagttttcat gg 22

<210> 480
<211> 18
<212> DNA
<213> Homo sapiens

<400> 480
catgtgatgg cgtgatcc 18

<210> 481
<211> 22
<212> DNA
<213> Homo sapiens

<400> 481
aggaatacac aaacaccgac ag 22

<210> 482
<211> 21
<212> DNA
<213> Homo sapiens

<400> 482
tgcaccctgt tttcttttct c 21

<210> 483
<211> 23
<212> DNA
<213> Homo sapiens

<400> 483
tggacaagta atggttttct ctg 23

<210> 484
<211> 21
<212> DNA
<213> Homo sapiens

<400> 484
tgacatttga gcaaagacct g 21

<210> 485
<211> 20

<212> DNA
<213> Homo sapiens

<400> 485
tttgttttgt tttgtttttt 20

<210> 486
<211> 27
<212> DNA
<213> Homo sapiens

<400> 486
ttacttatag gtttcaggag atgtgtt 27

<210> 487
<211> 23
<212> DNA
<213> Homo sapiens

<400> 487
gggtctttcg aatgtatgca atg 23